https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

See page 47 and 54 re Jap Biodistribution studies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Comirnaty : EPAR - Public assessment report (PDF/3.75 MB)
Adopted
First published: 23/12/2020

19 February 2021
EMA/707383/2020 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] * *Correction dated 19 February 2021 to clarify ERA statement*

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2021. Reproduction is authorised provided the source is acknowledged.

Table of contents

1. Background information on the procedure 8
1.1. Submission of the dossier 8
1.2. Steps taken for the assessment of the product 9

2. Scientific discussion 11
2.1. Problem statement 11
2.1.1. Disease or condition 11
2.1.2. Epidemiology and risk factors 11
2.1.3. Aetiology and pathogenesis 11
2.1.4. Clinical presentation and diagnosis 12
2.1.5. Management 13
2.2. Quality aspects 14
2.2.1. Introduction 14
2.2.2. Active Substance 15
2.2.3. Finished Medicinal Product 22
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 31
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 35
2.2.6. Recommendations for future quality development 39
2.3. Non-clinical aspects 41
2.3.1. Pharmacology 41
2.3.2. Pharmacokinetics 45
2.3.3. Toxicology 48
2.3.4. Ecotoxicity/environmental risk assessment 51
2.3.5. Discussion on non-clinical aspects 51
2.3.6. Conclusion on the non-clinical aspects 55
2.4. Clinical aspects 56
2.4.1. Introduction 56
2.4.2. Pharmacokinetics 58
2.4.3. Pharmacodynamics 58
2.4.4. Discussion on clinical pharmacology 66
2.4.5. Conclusions on clinical pharmacology 67
2.5. Clinical efficacy 67
2.5.1. Dose response study 67
2.5.2. Main study 67
2.5.3. Discussion on clinical efficacy 92
2.5.4. Conclusions on clinical efficacy 97
2.6. Clinical safety 98
2.6.1. Patient exposure 99
2.6.2. Reactogenicity 101
2.6.3. Adverse events 103
2.6.4. Serious adverse event/deaths/other significant events 108
2.6.5. Laboratory findings 109
2.6.6. Safety in special populations 109
2.6.7. Safety related to drug-drug interactions and other interactions 110

2.6.8. Discontinuation due to adverse events 110
2.6.9. Post marketing experience 110
2.6.10. Discussion on clinical safety 111
2.6.11. Conclusions on the clinical safety 114
2.7. Risk Management Plan 115
Safety Specification 115
Pharmacovigilance Plan 116
Routine pharmacovigilance activities 116
Additional pharmacovigilance activities 118
Overall conclusions on the Pharmacovigilance Plan 122
Plans for post-authorisation efficacy studies 122
Risk minimisation measures 123
Routine Risk Minimisation Measures 123
Summary of additional risk minimisation measures 123
Overall conclusions on risk minimisation measures 126
Summary of the risk management plan 127
Conclusion on the RMP 127
2.8. Pharmacovigilance 127
2.9. Product information 127
2.9.1. User consultation 127
2.9.2. Labelling exemptions 127
2.9.3. Quick Response (QR) code 129
2.9.4. Additional monitoring 129

3. Benefit-Risk Balance 130
3.1. Therapeutic Context 130
3.1.1. Disease or condition 130
3.1.2. Available therapies and unmet medical need 130
3.1.3. Main clinical studies 130
3.2. Favourable effects 131
3.3. Uncertainties and limitations about favourable effects 132
3.4. Unfavourable effects 132
3.5. Uncertainties and limitations about unfavourable effects 133
3.6. Effects Table 134
3.7. Benefit-risk assessment and discussion 135
3.7.1. Importance of favourable and unfavourable effects 135
3.7.2. Balance of benefits and risks 136
3.7.3. Additional considerations on the benefit-risk balance 136
3.8. Conclusions 138

4. Recommendations 139

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BDR	blinded data review
BLQ	below the level of quantitation
BMI	body mass index
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention (United States)
CGE	Capillary gel electrophoresis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	case report form
CRM	Clinical Reference Material
CRO	contract research organization
CSR	clinical study report
CV	curriculum vitae
C&E	Cause and Effect Matrices
DCT	data collection tool
DLS	Dynamic Light Scattering
DMC	data monitoring committee
DOE	Design of experiments
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
e-diary	electronic diary
EU	European Union
FIH	first-in-human
FSFV	first subject first visit
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCS	human convalescent serum
HCV	hepatitis C virus
HCV	Ab hepatitis C virus antibody
HIV	human immunodeficiency virus
HPLC-CAD	High-Performance Liquid Chromatography - Charged Aerosol Detector
IA	interim analysis
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
IPT-C	In-process testing control
IPT-M	In-process testing monitoring
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IVT	in vitro transcription
IWR	interactive web response
LAL	Limulus Amebocyte Lysate
LC-UV/MS	Liquid Chromatography – Ultraviolet / Mass Spectometry
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid

NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NMT	Not more than
NOR	Normal Operating Range
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PAR	Proven Acceptable Range
(q)PCR	(quantitative) Polymerase Chain Reaction
PD	protocol deviation
Ph.Eur.	European Pharmacopoeia
PPQ	Process Performance Qualification
PRM	Primary Reference Material
Prevax	prevaccination
PT	preferred term
QA	quality assurance
QA	Quality Attribute
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RT-PCR	Real Time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SMQ	standardized MedDRA queries
SOC	system organ class
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

TME	targeted medical event
TSE	Transmissible Spongiform Encephalopathy
UFDF	Ultrafiltration/diafiltration
US	United States
Vax	vaccination
VE	vaccine efficacy
WBC	white blood cell count
WCB	Working Cell Bank
WHO	World Health Organization
WRM	Working Reference Material
YOA	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioNTech Manufacturing GmbH submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Comirnaty, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication:

"Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of Comirnaty vaccine should be in accordance with official guidance."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0480/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0480/2020 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

New active Substance status

The applicant requested the active substance Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike

(S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product[2]

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibly to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	06 November 2020

[2] These steps do not reflect the additional submissions made by the applicant during the active assessment phases.

The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020.	15 December 2020
– A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020.	6 November 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Comirnaty on	21 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

2.1.2. Epidemiology and risk factors

Every individual is at risk of infection as there is no pre-existing immunity to the SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts.

According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

2.1.4. Clinical presentation and diagnosis

The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and subsequent multi-organ failure and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

The US Centres for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrheal
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. For example, in Italy the CFR was 0.3% in adults <40 years of age but 12.8% in adults 70 to 79 years of age and 20.2% in patients ≥80 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.5. Management

The management of COVID-19 has developed during 2020, and now includes antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins, anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a prophylactic vaccine during the ongoing pandemic, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic at a population level, e.g. to maintain a functioning health care system, and to avoid the social and economic consequences of the stringent measures needed to diminish virus spread. There is currently no approved vaccine in EU for prevention of COVID-19.

About the product

BNT162b is a mRNA vaccine for prevention of COVID-19. The vaccine is made of a mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The sequence of the S protein was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu-1", which was available when the program was initiated: GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein).

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2. The RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (see section 2.2). The LNPs protect the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (IM) delivery.

The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein is identified as a target for neutralising antibodies against the virus and is therefore considered a relevant vaccine component.

The vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) in two 30 µg doses of the diluted vaccine solution given 21 days apart.

Intended indication: *'Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older'*.

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

According to the Applicant, there is a positive benefit-risk balance for Comirnaty in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2, in individuals 16 years of age and older. This is based on evidence from the pivotal study C4591001 (also referred to as BNT162-02), a Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding Study investigating the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in healthy individuals.

The Applicant stated that the available data to date indicate that its vaccine was 95 percent effective and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant intends to continue the ongoing pivotal Phase 3 study with participants as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. In case of availability of any COVID-19 vaccine, the sponsor will appeal to participants to remain in the ongoing study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COMIRNATY in individuals <16 years of age have not been established for this application. Four studies in paediatric subjects are planned as laid down in the paediatric investigation plan. A study in pregnant women is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of Comirnaty (Study C4591010) will be conducted in the EU using primary data collection that monitors a cohort of vaccinees and evaluates risk of AESIs. The Applicant will also conduct, non-interventional studies (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 in a real-world setting. These studies will allow to determine the effectiveness of vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

- Unmet medical needs will be addressed

According to the Applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, Efficacy of COMIRNATY to prevent COVID-19 was demonstrated at the final analysis. The observed VE in each subgroup as defined by age, including elderly ≥ 65 years old, sex, race/ethnicity, country, obese subjects, and subjects at risk due to comorbidities, was overall consistent with the effectiveness of BNT162b2 to protect vaccinees against the disease. The benefit of immediate availability of Comirnaty through conditional marketing authorisation is based on the fact that there is no approved vaccine or successful COVID-19 therapy available in the European Union. An effective vaccine can impact the pandemic at this critical time and a COVID-19 vaccination program implemented soon can likely prevent further pandemic waves and thus substantially reduce mortality due to disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for dispersion for injection containing 225 µg/ 0.45 mL (prior to dilution) of BNT162b2 (5'capped mRNA encoding full length SARS-CoV-2 Spike protein) as active substance (AS).

Other ingredients are: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-

Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injections.

The product is available in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Pack size: 195 vials.

The multidose (5 dose) vial is stored frozen and must be thawed prior to dilution. After thawing, the vaccine should be diluted and used immediately.

After dilution with 1.8 mL sodium chloride (0.9%) solution (not supplied), one dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

2.2.2. Active Substance

General Information

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The vaccine is based on the spike glycoprotein (S) of SARS-CoV-2. The sequence was chosen based on the sequence for the "Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1". The protein sequence contains two proline mutation, which ensures an antigenically optimal pre-fusion confirmation (P2 S). The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. The applicant will provide clarification on the mechanism of action for BNT162b2.

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for both the Andover and the BNT Mainz & Rentschler manufacturing sites were provided.

The manufacturing process of BNT162b2 active substance involves five major steps. The RNA is synthesised from linear DNA via an in vitro transcription (IVT) step. The IVT step is followed by a number of purification and filtration steps. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen.

Flow diagrams were provided, presenting the process steps, process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The ranges of hold times and process parameters and routine in-process controls are listed with corresponding acceptance criteria, for each step. It is noted that not all process parameters are listed, but that the lists include all critical and several non-critical process parameters. It is agreed that the key process parameters are described in the dossier. The applicant has agreed to upgrade these parameters to critical process parameters (CPPs) and to include acceptable ranges for these CPPs. Updated information has been submitted during the procedure which comprised modifications of the acceptable ranges of several process parameters and the addition of some controls. The strategy is found acceptable, and the Applicant will provide information on acceptable ranges for some parameters.

The active substance is stored between -15°C and -25°C. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined. Shipping validation of the intermediate has been agreed as recommendation.

The batch numbering system is sufficiently described.

Control of materials

An adequate overview of the raw materials and solutions used in the active substance manufacturing process is provided.

Representative certificates of analysis have been provided. The submitted information supports the appropriate quality of raw materials. It is recommended that the applicant should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials **(REC1)** and should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases **(REC2).** The description of synthesis of 5'cap and its related impurities were requested during the procedure. Appropriate information was given. The applicant should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021 **(REC3)**.

The BNT162b2 active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells.

The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance. Changes to the manufacturing process of the linear DNA template (e.g. change to plasmid host cell) may result in a different impurity profile in the active substance. Additional details on the manufacturing process and the control strategy for this starting material, initially only shortly described, have been provided and the dossier will be updated accordingly.

The cell banks involved in the plasmid manufacturing process are described. Master cell bank (MCB) and working cell bank (WCB) qualification tests are listed. Relevant specifications are set and data from the current MCB and WCB are provided. The plasmid MCBs and WCBs are enrolled in a cell bank stability program. The strategy is considered adequate, noting that the dossier will be updated as appropriate. A protocol for establishment of future WCBs is provided.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. The strategy for establishing the initial shelf-life is endorsed and data provided support the proposed shelf life. A list of the raw materials as well as other materials used in the manufacture of the

linear DNA template is provided. All materials used are animal origin free and sourced from approved suppliers.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are routinely quantified. The reference material is described. Implementation of any changes in the manufacture of the linear DNA template should be applied for in a variation application.

Control of critical steps and intermediates

Process parameters and tests that are used to control the process and active substance quality are provided. The list of CPPs was provided with corresponding updated acceptable ranges.

A summary of the quality attributes with the rationale for the criticality assignment is provided. The rationale for classification into CQA or QA is presented for each attribute and appears reasonable.

The in-process test methods are defined and described in the dossier.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7).** The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6)**.

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

finished product manufacturing sites were validated to maintain product temperature in the acceptable range for a defined duration.

A transport verification study is planned and results will be available in Q1/2021. The recommendation to provide shipping performance qualification data has been agreed **(REC6)**.

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation **(SO1)**.

Regarding the 5’ cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute ‘capped-intact RNA’ is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5’-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5’-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

According to the Applicant, the majority of fragments are expected to be comprised of truncated transcripts including the 5’ region but lacking the 3’ region and poly(A)tail. However, the results indicating a substantial proportion of shorter/truncated mRNA with both cap and poly(A)tail are not in agreement with this statement. Therefore, the Applicant was asked to discuss and justify the obtained results and explain the apparent discrepancy. Additional characterisation data using an orthogonal method with enriched samples for fragmented species was provided. Preliminary characterization data on isolated fragmented species suggests they predominantly include the 5’-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction. The characterisation data are requested to be completed with analysis of the main peak from ion pairing RP-HPLC and analysis of other samples from Process 1 and optimised Process 2 **(SO1).** The Applicant will continue to evaluate any potential overestimation of poly(A) tail and should characterise fragments for any future AS process changes **(SO1)**.

Furthermore, the poly(A)tail of the 3’ end was characterised by LC-UV/MS. While the results were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified. As expected, poly(A) tail heterogeneity was observed both for Process 1 and Process 2 batches. Thus, slight differences in the poly(A)tail pattern were observed when comparing Process 1

and Process 2 AS batches. The Applicant explains that the redistribution is probably due to the use of a linearised DNA plasmid template in Process 2 instead of a PCR-derived DNA template in Process 1. For both processes, the poly(A)tail is anticipated to be sufficiently long to guarantee stability of the RNA and function in translation. This explanation is considered reasonable by the CHMP.

The overall primary sequence of BNT162b2 active substance was demonstrated to be comparable by LC/MS/MS -oligonucleotide mapping. Circular dichroism (CD) spectroscopy confirmed that the higher-order structure of Process 1 and Process 2 AS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 active substance was determined. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, further clarification is requested and include correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **(SO1)**.

A second comparability study was presented to assess comparability across the Process 2 manufacturing facilities, batches each from the Andover and BioNTech sites were included in the study. In addition, Process 2 batches, planned for clinical supply and for emergency supply in the US market and representative batches from Process 1 were included in the comparison.

In conclusion, the Process 2 batches manufactured at the Andover and BioNTech sites were demonstrated to be comparable with respect to identity as monitored by agarose gels and 5'Cap structure characterised by LC-UV and subsequent MS analysis. Furthermore, the primary sequence and the secondary structure was demonstrated to be comparable for all Process 1 and Process 2 batches included in the study. Poly(A) tail length and distribution was investigated by RP-HPLC and MS analysis. All process 2 batches were found comparable, while the Process 1 batches showed a somewhat different poly(A) tail pattern.

The expressed protein size after in-vitro expression of BNT162b2 active substance was determined and the results demonstrate comparability between batches. However, the identity of the bands identified by WB are not sufficiently justified and further clarification is requested **(SO1)**.

Overall, the submitted data confirm consistent and comparable quality of Process 2 batches manufactured at the Andover and BioNTech sites.

Process characterisation studies using scale-down models of individual unit operations, were performed.

It should be noted that future changes to any of the process parameters, regardless of the classification of CPP or non-CPP, should be applied for as variation to the terms of the MA.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following additional manufacturing campaigns and additional small-scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. It is noted that after the adjustment of these volumes, the percentage of RNA integrity has increased to levels more consistent with Process 1 batches. Nevertheless, since the target volumes for ATP and CTP have been increased to avoid that these nucleotides are rate-limiting in order to increase the percentage of RNA integrity, the PAR ranges need to be adjusted and the dossier updated accordingly **(REC8)**.

The acceptable ranges for CPPs will be updated in the dossier.

A safety risk assessment for potential process-related impurities included in the active substance process relative to patient safety was performed. The sources of the impurities are sufficiently addressed.

The safety risk assessment strategy involves comparison of the theoretical worst-case concentration of impurities, assuming no removal, to calculated safety concern thresholds.

The worst-case levels of residual raw materials and reagents from the BNT162b2 active substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable.

Characterisation

Analytical characterisation was performed on BNT162b2 active substance manufactured at commercial scale. This is found acceptable.

The physico-chemical characterisation involved primary structure, 5' cap structure, poly(A)tail and higher order structure evaluation. Primary structure was confirmed by oligonucleotide mapping and the orthogonal method, RNA sequencing using Next Generation Sequencing (NGS) technology. The results confirm the RNA sequence. The 5'-cap and 3' poly A tail were confirmed by two separate LC-UV/MS-methods. It was demonstrated that the predominant form of the 5' terminus is the full-length nucleotide sequence with the 5'-Cap. The higher order structure of BNT162b2 mRNA active substance was characterised in solution using biophysical techniques.

Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes. It is recommended that the applicant should comprehensively describe the capability of a specific analytical method to detect lower amounts of product related impurity in the presence of the correct form in the active substance. **(REC9)**.

An uncertainty in the characterisation section is that no biological characterisation is presented. In response to questions during the procedure, the applicant has committed to update dossier with the strategy for potency determination and to address relevant functional assays including the in vitro expression (potency) results and results from the analysis of expressed protein size for active substance lot 20Y513C101. It is recommended that the applicant should discuss the results and the assay suitability for a certain method used for biological characterization of protein expression for the active substance **(REC10)**.

As described above, the expressed protein size results are currently not sufficiently confirmed and a specific obligation is laid down in the terms of the MA requiring their adequate characterisation **(SO1).**

Process-related and product-related impurities as well as potential contaminants are described. A number of batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches from both manufacturing sites.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the active substance batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the AS specification in terms of RNA integrity. However, the characterisation of BNT162b2 AS is currently not found to be complete in relation to a specific parameter. This is especially important considering that the current AS and finished product acceptance criteria allow for a proportion of fragmented species. The Applicant should provide additional data to further characterise the truncated and modified mRNA species present in the finished product. Relevant protein/peptide characterization data for predominant species should be provided **(SO1)**.

Residual DNA template is a process-related impurity derived from the linearised DNA template added to the in-vitro transcription reaction. Residual DNA template is measured as defined in the active substance specification. The levels are controlled by a specification limit which is considered suitably low.

The potential contaminants described in this section are endotoxin and bioburden. Acceptable results are shown for the Proteinase K pool, UF retentate pre recovery, UF-product pool and the active substance, for all batches investigated.

Specification

The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for active substance is considered acceptable for authorisation with respect to the attributes chosen for routine release testing. During the procedure the specification limits for a number of attributes were tightened in response to questions.

The length of the poly(A) tails in BNT162b2 active substance is important for RNA stability and translational efficiency and even though comparable results have been reported to date, the poly(A) tail length should be included to the active substance release testing **(SO2)**.

The rationale used to establish the acceptance criteria is described in detail and based on a limited data set representative of BNT162b2 active substance manufactured at the intended commercial scale and process. From the available data, mRNA integrity, dsRNA and Poly(A) tail acceptance criteria are considered in relation with batches used in clinical studies and with the demonstrated manufacturing capability and need to be re-assessed and revised as appropriate as further data becomes available **(SO2).**

Potency testing is not included in the control of active substance but instead is performed at the level of finished product release testing. Considering the nature of this product, the approach is endorsed by the CHMP.

Analytical methods

All analytical methods used for testing of the active substance are sufficiently described in the dossier. The following tests are performed in accordance with Ph Eur chapters; clarity (Ph Eur 2.2.1), colour (Ph Eur 2.2.2), pH (Ph Eur 2.2.3), bacterial endotoxins (Ph Eur 2.6.14) and bioburden (Ph Eur 2.6.12).

All non-compendial analytical methods are sufficiently described. These analytical methods were suitably validated against the parameters presented in ICH Q2(R1).

The technical procedure for the quantification of the poly(A) tail is considered, in general, sufficiently described but the suitability of this method for the intended purpose remains to be confirmed **(SO2)**.

Batch analysis

Batch results are presented for active substance batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply and stability.

In general, the results obtained using the commercial process (Process 2) demonstrate batch to batch consistency with a few exceptions.

Reference materials

The current reference standard is referred to as the Clinical Reference Material (CRM). A stability protocol is provided. The Applicant has agreed to provide additional information such as protocol on preparation and qualification on the future reference material, as requested **(REC12)**.

In future, a two-tiered system for future commercial reference material will be implemented. A primary reference material (PRM) and an initial working reference material (WRM) will be established for the active substance reference material.

Container closure

The information regarding container closure system is acceptable. Compliance with Ph. Eur. has been verified.

Stability

Based on the limited stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system. The stability program is designed to follow ICH guidelines. The test methods used are stability indicating. Data from the sites Andover, Mainz, Rentschler are included.

It is noted that the Applicant states that testing is currently in progress on the clinical batches and the dossier will be updated with data for these batches, as well as any new data available for the primary process validation batches. Thermal cycling studies have been initiated and a minimum of one process validation batch will be subjected to photostability studies at a future date.

Based on the stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The BNT162b2 finished product (FP) is supplied as a preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the finished product at pH 6.9 - 7.9 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution to a total volume of 2.25 mL. Each dose contains 30 µg of RNA in 0.3 mL.

The overfill in the vial is required to ensure that the full five doses can be removed from the multi-dose vial after dilution and correctly administered, taking account of potential loss of product during these dilution and administration steps. The justification for the overfill is sufficiently discussed and considered to be acceptable. The applicant development data and finished product testing confirm that 5 doses can be consistently extracted from the vial and delivered after dilution.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The full list of excipients is listed above in section 2.2.1; ALC-0315 and ALC-0159 (functional lipids), DSPC and cholesterol (structural lipids), potassium chloride, potassium dihydrogen phosphate, sodium

chloride and disodium phosphate dihydrate (buffer components), sucrose (cryoprotectant) and water for injections.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply with Ph. Eur. The functional lipid excipients ALC-0315 and ALC-0159, are classified as novel excipients. Both structural lipids DSPC and cholesterol are used in several already approved finished products. A justification was provided for why DSPC is not considered to be a novel excipient. DSPC is used as part of the LNP for the EU approved finished product Onpattro which is administered intravenously in a much higher dose than the intramuscular dose for this product. Additionally; DOPC, a structurally related lipid, is present in finished products approved in the EU for intramuscular administration. It was therefore concluded that the level of information provided for DSPC, is in line with the requirements for a known excipient are sufficient and appropriately justified.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Formulation development

The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles. Furthermore, the accumulated batch-data to date show consistent manufacture of lipid nanoparticles both with respect to size and polydispersity.

Lipid-related impurities have been identified in the finished product and have been characterized. An investigation has been initiated and is ongoing to assess and review potential root causes. The outcome of the investigation shall be provided (SO2).

Visual particulate matter has occasionally been observed in finished product batches. Characterization data have been presented and the control strategy has been discussed. The data demonstrates that the particles are comprised of components of the finished product formulation. A 100% visual inspection is performed during manufacturing and the automatic inspection system is updated to improve the inspection. Routine release or routine stability data indicate that the propensity of particles to form following storage is low. If particles are observed in the diluted vaccine the vial should be discarded.

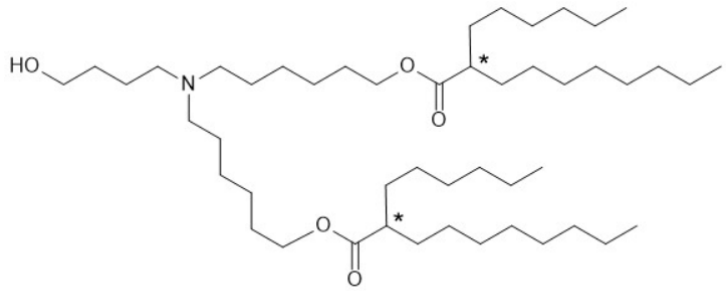
Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

Figure 1 ALC-0315 structure



Asterisks (*) indicate chiral centers.

A brief description of the chemical synthesis is provided. The suppliers are defined in the dossier. A similar manufacturing process is used for ALC-0315 in clinical and commercial finished product batches.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. (**SO4**)

The proposed specification is considered acceptable based on the available data. However, additional information regarding specifications that should be provided **(SO4)**.

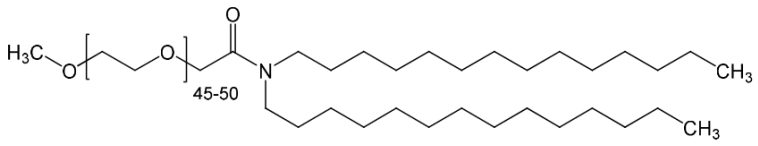
Stability data from one supplier indicate that ALC-0315 is stable when stored at the recommended storage conditions. Additionally, the excipient is stable at room temperature suitable for use in further manufacturing steps. Stability data from one supplier is considered representative for lipid from another supplier.

Lipid related impurities have been observed in some recently manufactured finished product batches, correlated with ALC-0315 lipid batches. The quality of ALC-0315 excipient is considered acceptable based on the available data on condition that specific impurities in the finished product will be further evaluated **(SO2)**.

ALC-0159 (PEGylated lipid)

The ALC-0159 novel excipient is a PEGylated lipid, 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

Figure 2 ALC-0159 structure



A brief description of the chemical synthesis is provided.

The suppliers are defined in the dossier. The same supplier was used during development for clinical phase 1, 2 and 3 studies. The same synthetic route was used for ALC-0159 throughout development of the finished product.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant is requested to provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **(SO5)**

The proposed specification is considered acceptable based on available data. However, in order to improve impurity control strategy and to ensure batch to batch consistency of the finished product, there are additional information regarding specifications that should be provided **(SO5)**.

Stability data indicate that ALC-0159 is stable when stored at the recommended storage conditions.

Manufacturing process development

The development history of the finished product is sufficiently described. The process has been transferred to commercial facilities for manufacture of later clinical materials, emergency supply and commercial supply. A table on finished product lot genealogy and usage has been provided.

The applicant states that comparability is demonstrated in a stepwise approach through a combination of release testing and extended characterization methods. It is agreed that comparability was sufficiently demonstrated with only small differences noted.

During the present regulatory procedure, release testing results of a number of recently manufactured GMP-batches was presented. The release data for the GMP-batches are compared to the clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification and that comparability has been sufficiently demonstrated subject to the specific obligations further described, for the attributes tested and given the pandemic situation. In addition, the comparison will be further extended with additional characterization testing on future batches of finished product. The applicant has confirmed that testing will be performed according to the agreed finished product comparability testing protocol and the results will be submitted in the frame of a specific obligation (**SO3**).

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented and is agreed. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program at the commercial facility has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data (**SO3**).

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies using scale-down models of individual unit operations, were performed.

Overall control strategy was presented but some parameters and ranges may be updated after PPQ and additional characterization studies completed. As for assessment of overall control strategy, a complete set of data and information is needed, this document will be assessed when finalised. A time-plan for the provision of the final data set has been agreed with the applicant **(SO3)**.

The analytical testing strategy of finished product has changed throughout the development and these changes have been described. Bridging studies have been performed for analytical tests that have been changed or replaced (subvisible particles, identity of encoded RNA sequence and RNA integrity). This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The primary packaging is composed of glass vial and rubber stopper and are compliant with the compendial requirements of Ph. Eur.

Controlled extraction studies have been performed on the bromobutyl rubber stopper. The applicant will provide the updated results from the leachables study for assessment. (**REC13**)

Microbiological attributes

Container closure integrity testing has been performed to demonstrate that the 2 mL container closure presentation is integral.

In order to improve the control strategy, the MAH should provide validation results of alternative sterility test i.e. rapid sterility test for assessment before implementation (**REC14**).

Compatibility

The studies described have been performed to assess physicochemical stability of the FP after dilution with 0.9% sodium chloride solution in the original glass vial as well with commonly used commercially available administration components and using worst-case conditions for dosage and administration in the clinical setting. The thawed hold time (in-use period) of undiluted finished product has been defined as 5 days at 2-8 °C and 2 hours at up to 30 °C.

Results presented support physicochemical stability of FP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures (2-30°C) following an in-use thawed hold time of up to 5 days at 2-8 °C and 2 hours at 30 °C.

Compatibility with dosing components (syringes and needles) has been established for up to 6 hours. Furthermore, a microbiological in-use hold time study has been performed by a challenge test including five compendial micro-organisms. No significant growth (>0.5log10 from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted FP in 0.9% sodium chloride solution. Therefore, based on the results from the microbiological in-use hold time study, the proposed in-use period for up to 6 hours at ambient temperatures is agreed, as reflected in the product information. Furthermore, it is also stated by the applicant that the in-use period is in alignment with the WHO policy on the use of opened multi-dose vaccine vials (WHO Policy Statement: Multi-dose vial policy (MDVP) – handling of multi-dose vaccine vials after opening, rev 2014).

The compatibility of finished product is acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

The finished product is batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium or BioNTech Manufacturing GmbH, Mainz, Germany. The GMP status of the manufacturing and testing sites of the finished product have been confirmed.

The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Dossier should be updated to provide more details on increase batch size including range number of AS bag and batches used, configuration of filters filter surfaces used and process controls (**REC14**). The absence of a test for residuals is considered acceptable.

Shipping validation

This section gives a summary of the qualification of the shipping process for transport of BNT162b2 finished product by passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60 °C from the finished product manufacturing and packaging site to dosing sites in the EU.

Short periods of time outside of the intended routine shipping condition of -90 to -60 °C during transport and at distribution sites have been defined.

The shipping temperature range of -90 to -60 °C is based on available stability data.

One thaw and refreeze cycle is allowed during transportation. Time during transportation out of the intended storage and shipping temperature range (-90 to -60 °C) without thaw is allowed for specified times and conditions for multiple transfers and redistribution during shipping with subsequent refreezing to -90 to -60 °C between transfers. The temperature excursion allowances are supported by data.

The selected shipping methods include shipping containers designed to maintain product temperature through a combination of insulation and dry ice. The applicant has prior experience with these passive thermal conveyances and has demonstrated that they maintain the -90 to -60 °C temperature range during product shipments, including minor shipping delays and short exposures to extreme temperatures occasionally observed during shipping and handling.

All shipments are continuously monitored using temperature data loggers.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal conveyance, supported by operational qualification and performance qualification testing. A summary of the shipping qualification strategy has been provided.

For the passive thermal conveyance, the qualification is focused on the ability of the passive system to maintain the required temperatures with specified phase change materials or dry ice when exposed to ambient temperature profiles for worst-case season. These studies are carried out in laboratory chambers to simulate the summer as worst-case ambient profiles.

A simulated distribution study demonstrated finished product and package integrity after exposure to simulated distribution hazard conditions, following the durations outlined in the worst-case extended transport lanes.

Results of thermal qualification have met specified acceptance criteria and support shipments of BNT162b2 finished product using the passive thermal conveyance shipping containers either directly or

via qualified distribution centres. Passive thermal conveyance performance qualification and the simulated shipping study finished product impact testing have been performed to complete shipping qualification assessing both thermal and mechanical aspects of shipping.

Process parameters for storage and shipping are found acceptable.

Media fills

Media fills have been performed for the filling line to validate the aseptic filling process and were run in accordance to guidelines. Results have been provided from three consecutive simulation studies and gave satisfactory results without any contaminated units. Results for the media fill cover the maximum process time for the manufacturing of finished product and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process. For the filling line, the maximum time will be established upon completion of media fill qualification studies. This is found acceptable.

Verification of in-process test methods

Data on verification of in-process test methods was pending at the time of the present regulatory procedure and should be provided during Q2 2021 (**REC15**).

Hold times

Hold times have been established. It is noted that any change of this section needs to be submitted to the Agency via a variation application.

Process validation plan

A FP process validation plan has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

It is described in the dossier that commercial scale PPQ-batches will be manufactured during Dec 2020 to Jan 2021 and the applicant has provided a process validation plan. In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation data, by March 2021. (**SO3**)

Filter validation

Acceptable information has been provided during the procedure for filter validation on the filters used for sterile filtration, describing the material, pore size and surface area. All study results met the predetermined acceptance criteria and the studies for microbial retention, membrane compatibility, extractable substances and integrity test determination have shown that the filters are appropriate for sterile filtration of the finished product. In addition, the applicant has clarified that the filter used for bioburden reduction is identical to the filters used for sterile filtration.

The MAH should provide the results for assessment from the filter validation as soon as they are available (**REC23**).

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved finished product within EU. Additional information is provided separately in Section A.3 of the dossier.

DSPC is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is sufficiently controlled according to the Ph. Eur. monograph with additional tests for residual solvents and microbial contamination.

The other excipients (sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection) are controlled according to respective Ph. Eur. monograph.

The processing aids ethanol and citrate buffer are controlled according to Ph. Eur. standards and for HEPES and EDTA, reference is made to the active substance.

Product specification

The release and stability testing specifications for BNT162b2 finished product include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications document for finished product in section 3.2.P.5.1 of the dossier includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmolality, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at FP release, all other analytical procedures are conducted at release and stability studies for finished product. It is stated by the applicant that the acceptance criteria used for stability during shelf-life will be the same as the acceptance criteria used for lot release.

Several questions in relation to the acceptance criteria in the FP specifications were raised during the procedure (i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity). The acceptance criteria were tightened.

For potency, RNA integrity, RNA encapsulation, lipid content and polydispersity index, the acceptance criteria will be re-assessed during Q2 2021 in order to ensure a consistent product quality by providing additional information to enhance the control strategy. This is found acceptable subject to a specific obligation. (**SO2**)

The vial contains an overfill in order to ensure that the full required volume (5 doses) can be delivered following dilution and administration in line with the product information. The finished product specification includes a test to confirm the extractable volume from the vial provides 5 doses. During the procedure the applicant proposed to update the product information and instructions for use to indicate that up to 6 doses can be delivered from the vial. This proposed change to the product information was not considered acceptable as no supporting data were provided to demonstrate that 6 doses can be consistently extracted. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses (**REC21**).

A risk evaluation regarding the risk of N-nitrosamines impurities was provided concluding that there is no risk of the presence of nitrosamines in the finished product taking into account the active

substance, the finished product formulation and primary packaging. The risk assessment is considered acceptable.

It is recommended that a risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D **(REC17)**.

A question was raised during the procedure since no information and discussion was provided in the dossier on lipid-related impurities originating from the degradation of the LNP. It is argued by the applicant that with respect to potential lipid-related impurities originating from the degradation of LNPs, no degradation of the LNP FP has been observed in the stability studies at the recommended storage temperature (-70 to -90 °C) for the LNP as shown by specifications for size and polydispersity, RNA encapsulation, RNA and lipid content and RNA integrity quality attributes. This is acknowledged. In addition, further evaluation of lipid-related impurities in the finished product should be performed and the results submitted and discussed in the frame of a specific obligation (**SO2**).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The dossier includes release testing results of four recently manufactured GMP-batches. These finished product GMP batches were manufactured at the commercial FP manufacturing site. The release data for these GMP-batches are compared to min-max ranges of the small-scale clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification. Therefore, it can be concluded that comparability has been sufficiently demonstrated for the attributes tested given the pandemic situation and considering that further data is to be provided in the frame of a specific obligation. In addition, the comparison will be further extended with additional characterization testing on future PPQ-batches of finished product. The applicant has confirmed that testing will be performed according to the finished product comparability testing protocol. and the results will be provided in the frame of specific obligation **(SO3)**.

Reference materials

The finished product reference materials is the same as for active substance.

Stability of the product

A shelf-life of 6 months for the finished product is proposed when stored at the recommended storage condition of -90°C to -60°C.

The applicant has provided stability results up to 6 months at -80 to -60°C of one clinical batch and up to 6 months of a non-clinical batch of finished product. Two weeks data are also provided for two emergency supply under recommended storage conditions. In addition, there are newly initiated stability studies on the recently manufactured GMP-batches as well as plans to initiate stability studies on the future PPQ-batches.

Stability data have also been provided at accelerated (-40°C to +5°C) and stressed (+25°C to +30°C) storage conditions.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological products: Stability testing of biotechnological/biological products) and the same or representative container-

closure system are used in these stability studies as will be used for commercial batches. The test methods used are stability indicating.

Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality at the recommended storage condition (-90 to -60°C).

The applicant has provided updated reports from the ongoing stability studies and the presented data are considered sufficient and in support of the shelf-life claim since comparability has been sufficiently demonstrated between commercial scale GMP batches and the small-scale clinical batches.

In addition, the initial in-use period for the thawed, undiluted vial is 5 days at 2-8°C followed by storage at up to 30°C for not more than 2 hours. This is found acceptable.

Chemical and physical in-use stability has also been demonstrated for 6 hours at 2ºC to 30ºC after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection.

It is described that the future PPQ-lots will be enrolled in the stability program and the stability protocol has been defined in the dossier. This is acceptable; however, the applicant should commit to provide the 6 months stability data for the PPQ-batches for assessment as soon as they are available. (**REC20**). Notwithstanding requests for further stability updates, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

It has been clarified by the applicant that results on photostability testing studies will be provided for assessment (**REC19**).

It is recommended that the applicant should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70°C to -20°C. In addition, the applicant should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8°C as well as the possibilities to extend the claims for transport conditions at 2-8°C **(REC22)**.

A shelf-life of 6 months for the finished product at -90 to -60°C is accepted.

Adventitious agents

Adventitious agents' safety evaluation has been provided for the AS manufacturing sites and for the finished product manufacturing site.

Reagents used in active substance manufacturing and in the establishment of the MCB and WCB are the only materials of animal origin used in the manufacture of BNT162b2. The applicant has identified contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents as the main theoretical risk associated with these ingredients and it is deemed of minimal risk.

Additional clarifications were requested and provided for a number of other materials.

Sufficient details on the aseptic validation filling and media fills have been provided. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process. Therefore, no additional concerns are raised.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the absence of validation data on finished product manufactured at the commercial site. These issues were classified as Major Objections (MOs).

After further information was obtained from the sites and inspectors, questions regarding the manufacturing were addressed and manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing and testing sites.

Some of the proposed sites for batch control testing are currently located in the USA. The following time-limited derogation has been introduced as a condition to the MA:

'*In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application'.*

Additional data have been submitted by the applicant during the procedure in response to the other MOs and other questions raised.

Having considered the emergency situation and the quality documentation provided, the CHMP imposed some specific obligations (SOs) with clearly defined due dates (refer to Conclusions for details). In addition, the CHMP adopted some Recommendations (RECs) to be addressed by the Applicant.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

Overall, the information provided is satisfactory. However, certain information is still pending due to the very short time frame of product development and will either be updated in the dossier imminently or further addressed in specific obligations and other post-approval measures.

Information on the manufacturing process and process controls for the manufacturing sites Andover and BNT Mainz & Rentschler have been provided and are considered satisfactory.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: increased process scale, DNA template changed from a PCR template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UFDF steps. Based on the differences observed between batches manufactured by active substance Process 1 and 2 for the CQA mRNA integrity and lack of characterisation data, a MO was raised regarding comparability, characterisation and clinical qualification of the one proposed acceptance criteria. Biological characterisation of the active substance was limited, and additional data and discussion were requested to address functionality. Additional characterisation data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay **(SO1).**

Truncated RNA species are regarded as product-related impurities and can be expected due to the principle of the in-vitro transcription reaction (i.e. directional polymerase activity) and (theoretical) hydrolysis during manufacturing. Analysis of RNase treated samples showed that all species detected

by the capillary gel electrophoresis (CGE)-based method are composed of RNA. Manufacturing consistency with respect to fragmented species has been sufficiently demonstrated.

There were some differences in truncated RNA species level, however further analyses revealed a comparable overall fragmentation profile among Process 1 and Process 2 active substance batches. Additionally, oligonucleotide mapping data demonstrated no significant differences observed between Process 1 and Process 2 active substance batches.

The company does not expect truncated transcripts formulated in the finished product to pose a safety or efficacy concern, as in their view no protein expression is expected from truncated transcripts. Further, clinical trials with process 1 material have not revealed major safety concerns to date. Truncated BNT162b2 RNA species lacking either the 5' cap or the poly(A) tail are expected to be rapidly targeted for degradation in the cytoplasm or would show a decrease or loss of translation efficiency. Preliminary characterization data on isolated fragment species suggest that fragment species predominantly include the 5'-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction.

However, as the overall characterisation of the truncated species is still limited, additional analysis of truncated species, additional translated protein characterisation, additional characterisation of lipid-related impurities and potential lipid-RNA species should be provided to support that they are not impacting clinical performance in terms of safety and/or efficacy. The current specification allows for a certain level of truncated mRNA species to be present however data from recent batches have shown levels of truncated species below that level. No related safety issues have been identified in the clinical studies thus far in subjects who received vaccine containing up to a certain level of truncated species. Therefore, the current specification is considered acceptable subject to the submission of additional data in the frame of a specific obligation (**SO1**).

Based on available data, the proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing. However, the length of the poly(A) tails in BNT162b2 active substance is critical for RNA stability and translational efficiency and therefore should be introduced in active substance release testing in the frame of a specific obligation (**SO2**). Moreover, the active substance specification acceptance limits should be re-assessed and revised as appropriate, as further data become available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

It is noted that the Applicant states that testing is currently in progress on the clinical batches and data for these batches, as well as any new data available for the primary process validation batches, will be provided. Based on the limited stability data presented, a shelf-life is approved for the active substance.

Finished product

The finished product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described including studies that were performed with available active substance, representative of the mRNA platform and included in the finished product.

The development of the manufacturing process is extensively described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication and bulk finished product formulation followed by fill and finish, and the process has been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for the attributes tested and will be subject to a specific obligation.

Limited data on the finished product batches manufactured at the commercial facility (entire manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, active substance from process 2) were presented. A process validation plan for PPQ lots has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program, also comprising the commercial facility at Puurs, Belgium, has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(SO3).**

The specifications for finished product include a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised, i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity. Whilst FP specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

Two novel excipients are included in the LNP. Complete information is not provided for both the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. In order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch to batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with specific obligations **(SO4, SO5).**

Lipid-related impurities have been observed in some recently manufactured finished product batches. For the batches with lipid-related impurities the existing quality control parameters including RNA integrity remain unchanged.

Considering the above and the emergency situation, the characterisation of the active substance and finished product is considered acceptable, and the proposed specifications for RNA Integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. These data are requested to be provided as specific obligations to the applied conditional marketing authorisation **(SO1, SO2)**.

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine from Process 1. The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities. The suitability of the analytical methods used for control of potency and poly(A) tail have not been fully demonstrated.

Data demonstrate the presence of significant amounts of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are poorly characterised, and the limited data provided for protein expression do not fully address the uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein.

The control strategy for active substance and finished product is important to guarantee acceptable quality and ensure batch to batch consistency of the finished product. Regarding the proposed control strategy, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Truncated and modified RNA are present as impurities. Considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell there is a possibility that aberrant proteins will be expressed with possibilities for unwanted immunological events. The risk of this occurring is considered low based on the following observations and considerations:
    - Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
    - The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA.
    - The level of any individual aberrant mRNA species would in any way be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The amount of the protein would be expected to be too low to elicit an immune response. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the aberrant protein would be non-significant.
- Lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to the specific obligations abovementioned.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While the characterisation data still

need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In addition, and in accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

In the context of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs):

- SO1: In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. **Due date: July 2021. Interim reports: March 2021.**
- SO2: In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. **Due date: July 2021. Interim reports: March 2021.**
- SO3: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data. **Due date: March 2021.**
- SO4: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **Due date: July 2021, Interim reports: January 2021, April 2021.**
- SO5: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **Due date: July 2021, Interim reports: January 2021, April 2021.**

As regards SO1, the following data are requested in order to complete the information on the active substance and finished product characterisation.

a) Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into

truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. **Due date: July 2021. Interim reports: March 2021, and on a monthly basis.**

b) The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail. **Due date: July 2021. Interim report: March 2021**

c) Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **Due date: July 2021. Interim report: March 2021**

As regards SO2, the following data are requested to be provided in order to ensure a comprehensive control strategy, including active substance and finished product specifications:

a) The active substance and finished product specifications acceptance limits, should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. **Due date: July 2021, Interim reports March 2021, and on a monthly basis.**

b) Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set. **Due date: July 2021, Interim reports: March 2021**

c) The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes. **Due date: July 2021, Interim reports: March 2021**

d) Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability. **Due date: July 2021, Interim reports: March 2021.**

e) Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. **Due date: July 2021, Interim reports: March 2021**

f) Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021. **Due date: July**

2021, Interim reports (LMS content in commercial FP batches, investigation results): March 2021, and on a monthly basis.

As regards SO3, the following data are requested to be provided in order to ensure batch to batch consistency and to complete the information on process validation of the finished product manufacturing process.

a) Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities. **Due date: March 2021.**

b) The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment. **Due date: March 2021.**

As regards SO4, the data are requested to be provided regarding the synthetic process and control strategy for the excipient ALC-0315 in order to improve the impurity control strategy, assure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product.

a) A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed **by July 2021. Interim report: January 2021**

c) Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. **Due date: July 2021, Interim report: January 2021**

d) Information and justification on critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate. **Due date: July 2021**

g) The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product. **Due date: July 2021**

h) Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided. **Due date: July 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

As regards SO5, the following data is requested to be provided regarding the synthetic process and control strategy for ALC-0159 in order to improve impurity control strategy, assure comprehensive control and batch-to-batch consistency throughout the lifecycle of the active product.

a) A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG. **Due date: July 2021, Interim report: January 2021**

c) Information and justification of critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

d) The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product. **Due date: July 2021, Interim report: April 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate. **Due date: July 2021**

g) Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis. **Due date: January 2021**

h) Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided. **Due date: July 2021, Interim report: April 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

2.2.6. Recommendations for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1. The MAH should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials.
2. The MAH should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases.
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.
4. The MAH should reassess the specification for the linear DNA template purity and impurities. The Applicant has already agreed to supply these by Q2 2021.
5. The MAH should perform and document a gap analysis to identify any supplemental qualification needed to align the methods used for the DNA template control with ICH requirements. The gaps identified should be addressed either prior to transferring the methods to relevant sites or during the transfer activities.
6. The MAH should provide active substance process validation data regarding the finalised

indirect filter qualification assessment and the shipping validation between sites.

7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step.
8. The MAH should tighten the low limits of the proven acceptable ranges for the target volumes for ATP and CTP, to the levels needed to ensure a sufficiently high mRNA integrity in the active substance manufacturing process.
9. The MAH should comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance.
10. The MAH should discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterization of protein expression for the active substance.
11. The MAH should provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in BNT162b2 active substance.
12. In order to improve the control strategy, the MAH should provide the protocol on preparation and qualification of future primary and working reference standards for the active substance.

Finished Product

13. The updated results from the finished product leachables studies should be provided for assessment.
14. In order to ensure batch to batch consistency of the finished product the MAH should expand the description of the manufacturing process with more details. (1) When the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated. (2) The MAH should confirm the configuration of filters used in finished product manufacture. (3) The surface area of the sterile filter should be adapted to the batch size, unless otherwise justified; (4) process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes
15. Data on verification of in-process test methods should be provided for assessment during Q1 2021.
16. In order to improve the control strategy, the MAH should provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation.
17. A risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). A summary of this risk assessment should be submitted. The risk assessment should cover all relevant elements and sources in accordance with the guideline. The summary must enable a quantitative comparison of observed or predicted levels with the PDE's given in the guideline. It should contain what is necessary to evaluate the appropriateness and completeness of the risk assessment, including any assumptions, calculations etc. made. The control strategy for elemental impurities should be justified based on the risk assessment.
18. The MAH should provide the protocol on preparation and qualification of future primary and working reference materials for finished product testing.
19. In order to provide further information regarding the stability of finished product, Results from photostability testing and temperature cycling studies of the finished product should be provided for assessment in Q1 2021.
20. The applicant should provide the 6 months stability data for the finished product process performance qualification batches for assessment as soon as they are available.
21. This applicant proposed change to the product information to indicate that up to 6 doses can

be delivered from the vial was not considered acceptable as no supporting data was provided. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses.

22. The MAH should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70 °C to -20 °C. In addition, the MAH should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8 °C as well as the possibilities to extend the claims for transport conditions at 2-8 °C.
23. The MAH should provide the results for assessment from the filter validation as soon as they are available.

2.3. Non-clinical aspects

GLP inspections

The pivotal toxicological studies are stated to be GLP compliant by the Applicant. There were some issues identified during the assessment with repeat-dose toxicity study #38166 regarding the documentation which have led to a study audit GLP inspection conducted by the local German GLP Compliance Monitoring Authority at the facility where the study was performed, in November 2020. All the answers to the issues were acknowledged by the CHMP. The Applicant gave also comments on these issues. In light of all the elements provided, the issues identified were considered resolved.

With regard to repeat-dose toxicity study #20GR142 the only major concern identified was resolved with the answers from the Applicant that were considered satisfactory by the CHMP.

2.3.1. Pharmacology

The pharmacology dossier is based on initial studies of the functionality of the BNT162b2 (V9) RNA-based product and the encoded SARS-CoV-2 P2 S protein as well as on supporting studies of SARS-CoV-2 P2 S protein structure. This is followed by characterisation of the humoral and cellular immune response in mouse and nonhuman primate upon immunization with BNT162b2 (V9) and ends up with a SARS-CoV-2 challenge study of BNT162b2 (V9) immunized nonhuman primates.

No secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies have been conducted with BNT162b2 due to the nature of the RNA-based vaccine product, which is according to applicable guidelines (WHO guideline on nonclinical evaluation of vaccines, WHO Technical Report Series, No. 927, 2005).

Mechanism of action

SARS-CoV-2 infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, of which the angiotensin converting enzyme 2 (ACE2) may constitute a major part, as recently suggested. In addition to the initial attachment to a host cell, the S protein is also responsible for viral envelope fusion with the host cell membrane resulting in genome release. Due to its indispensable role, the S protein is a major target of virus neutralizing antibodies and has become a key antigen for vaccine development. By immunisation with the modified RNA (modRNA) product BNT162b2, encoding for the S protein, the intention is to trigger a strong and relatively long-lasting production of high affinity virus neutralizing antibodies, which can act through blocking the S-protein and it's receptor-binding domain (RBD) interaction with host cell receptors but also by opsonisation mediated virus clearance. In addition, the immunisation with BNT162b2 is also intended to elicit a concomitant T cell response of the Th1 type, supporting the B cells responsible for the production of S-specific antibodies and cytotoxic T cells that kill virus infected cells.

The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation before engaging with a target cell. BNT162b2 encodes a P2 mutant (P2 S) variant of S where two consecutive proline mutations have been introduced in order to lock the RBD in the prefusion conformation. In addition, BNT162b2 is nucleoside-modified by a substitution of 1-methyl-pseudouridine for uridine and thus its inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors (TLRs) 7 and 8, is dampened, but not abrogated. Furthermore, the structural elements of the vector backbones of the BNT162b2 are optimised for prolonged and strong translation of the antigen-encoding RNA.

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al, 2019; Patel et al, 2019); ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface. The composition of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity.

Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Primary pharmacodynamic studies

Primary pharmacodynamic studies in vitro

To confirm the functionality of the BNT162b2 (V9) RNA-based product, protein expression, transfection frequency from BNT162b2 and cell surface expression of the SARS-CoV-2 P2 S protein antigen was assessed. BNT162b2 (V9) transfection of HEK293T cells indicated SARS-CoV-2 P2 S was correctly expressed on the cell surface, as indicated by flow cytometry staining of non-permeabilized cells with an anti-S1 monoclonal antibody. In addition, the cellular localisation of expressed S1 protein was investigated. The S protein co-localized with an ER marker, as detected by immunofluorescence experiments in HEK293T cells expressing BNT162b2-RNA, suggesting the S protein is processed within the ER.

In a set of supportive studies, it was investigated whether BNT162b2 RNA encodes for an amino acid sequence that authentically express the ACE2 binding site (RBD). Recombinant P2 S was expressed from DNA encoding for the same amino acid sequence as BNT162b2 RNA encodes for. Flow cytometry staining with spike protein (S) binding agents, as human ACE2 and monoclonal antibodies known to bind to authentic S-protein all indicated an authentically presented P2 S protein and ACE2 binding site. Low nanomolar affinity of P2 S binding to ACE2 PD and B38 mAb was demonstrated with the use of biolayer Interferometry.

To further structurally characterize the P2 spike protein, a cryo-electron microscopy (cryoEM) investigation of purified P2 S, expressed from DNA, was conducted. The cryoEM revealed, according to

the Applicant, a particle population closely resembling the prefusion conformation of SARS-CoV-2 spike protein. By fitting a previously published atomic model on to a processed and refined cryoEM dataset, a rebuilt model was obtained showing good agreement with reported structures of prefusion full-length wild type S and its ectodomain with P2 mutations. In the prefusion state the RBD undergo hinge-like conformational movements and can either be in an "up" position (open for receptor binding) or in a "down" position (closed for receptor binding). Three-dimensional classification of the dataset showed a class of particles that was in the conformation one RBD 'up' and two RBD 'down". This partly open conformation represented 20.4% of the trimeric molecules. The remainder were in the all RBD 'down' conformation. Although potent neutralizing epitopes have been described when the RBD is in the "heads down" closed conformation, the "heads up" receptor accessible conformation exposes a potentially greater breadth of neutralizing antibody targets. It is concluded that antibodies to both the up and down conformations will potentially be formed upon immunisation with the P2 S encoding BNT162b2.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates. The choice and relevance of the mouse for pharmacological animal model studies was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Non-human primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. The selection of rats as the toxicology test species is consistent with the World Health Organization (WHO) guidance documents on nonclinical evaluation of vaccines (WHO, 2005). The documents recommend conducting vaccine toxicity studies in a species which mounts an immune response to the vaccine. The Wistar Han (WH) rat developed an antigen-specific immune response following BNT162b2 vaccination.

Balb/c, females were immunized IM on day 0 with 0.2, 1 or 5 µg RNA/animal of BNT162b2 (V9), or with buffer alone (n=8). Blood samples were collected on Days 7, 14, 21 and 28 after immunization. The IgG antibody response to SARS-CoV-2- RBD or S1 was analysed by ELISA. Immunization with BNT162b2 induced IgGs that bound to S1 and RBD, as detected by ELISA, and on day 28 after immunization showed a binding affinity of KD 12 nM or 0.99 nM (geometric mean) respectively, as detected by surface plasmon resonance.

To further characterise the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virus type neutralization assay (pVNT) was used as a surrogate of virus neutralization since studies with authentic SARS-CoV-2 requires a BSL3 containment. The pVNT was based on a recombinant replication-deficient vesicular stomatitis virus (VSV) vector that had been pseudotyped with SARS-CoV-2 S protein according to published protocols. A dose-dependent increases in SARS-CoV-2-S VSV pseudovirus neutralizing antibodies were observed in sera from BNT162b2-immunized mice. On day 14, the difference of the group treated with 5 µg RNA compared to the buffer control was statistically significant ($p = 0.0010$). On days 21 and 28, the differences of the groups treated with 1 µg and 5 µg BNT162b2 compared to the buffer control were statistically significant. The relevance of the pseudovirus assay for authentic SARS-CoV-2 was not discussed. For technical reasons, it was not possible to determine a ratio of neutralizing to non-neutralizing antibodies.

Immunisation of mice with BNT162b2 also induced IFN-γ secreting cells of both the CD4+ and CD8+ T-cell subsets. This was shown by ELISPOT after *ex vivo* re-stimulation of splenocytes with an S-protein overlapping peptide pool Day 28 after immunization. Cytokine profiling was also carried out by Multiplex analysis of cytokine release from the Day 28 Splenocytes. High levels of the Th1 cytokines IFNγ and IL-2 but minute amounts of the Th2 cytokines IL-4, IL-5 and IL-13 were detected after re-stimulation with S but not RBD overlapping peptide mix. The much higher immune cellular responses

elicited against the S1 protein compared to the RBD domain could be explained by the presence of significantly more T cell epitopes in the larger full-length S peptide mix (in addition, S1 covers the RBD domain). It should be emphasized that cellular immune reactivity is much more important against S1 than against the RBD domain, where neutralizing antibodies are more important to the latter. In addition, an elevated secretion of TNFα, GM-CSF, IL-1β, IL-12p70 and IL-18 was recorded after re-stimulation. In order to characterize the immunophenotype of B-and T-cells appearing in lymph nodes from mice immunized with BNT162b2 (V9), B- and T-cell subsets in draining lymph node cells were quantified by flow cytometry 12 days after immunization. Higher numbers of B cells were observed in the samples from mice that received BNT162b2 compared to controls. That included plasma cells, class switched IgG1- and IgG2a-positive B cells, and germinal centre B cells. T-cell counts were elevated, particularly numbers of T follicular helper (Tfh) cells, including subsets with ICOS upregulation, which play an essential role in the formation of germinal centres (Hutloff 2015).

In the nonhuman primate (rhesus macaques) studies, BNT162b2 (V9) was shown to be immunogenic after intramuscular administration. The serum concentrations of both S1-binding and the SARS-CoV-2 neutralizing antibody titres were at least an order of magnitude higher after BNT162b2 immunization of rhesus macaques than for the panel of SARS-CoV-2 convalescent human sera. In this study, total antibody response is measured using a luminex assay and results expressed on U/ml and for the neutralization assay results are expressed in VNT 50.

Antigen specific S-reactive T-cell response after BNT162b2 immunization of the macaques was measured by ELISPOT and ICS. While S-specific T cells were low to undetectable in naïve animals, strong IFNγ but minimal IL-4 ELISpot responses were detected after the second 30 or 100 µg dose of the BNT162b2. Intra cellular staining (ICS) confirmed that BNT162b2 immunization elicited strong S-specific IFNγ producing T cell responses, including a higher frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-alpha but a lower frequency of CD4+ cells that produce IL-4. An S-specific IFNγ producing CD8+ T cell response was also recorded.

A challenge study in rhesus macaques was conducted as nonclinical proof of concept (PoC). Rhesus macaques share a 100% homology with the human ACE2 sequence that interacts with the RBD of the S protein. BNT162b2 (V9) immunized macaques were challenged with SARS-CoV-2 intra nasally and intratracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21, in order to align with the clinical vaccination regimen. Some other COVID-19 vaccine candidates have different prime-boost intervals, such as 4 weeks for both ChAdOx1 (Graham et al., 2020) and mRNA-1273 (Corbett et al., 2020). At the time of challenge, SARS-CoV-2 neutralising titres ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralising titres were undetectable in animals from the control-immunized and sentinel groups. The presence of SARS-CoV-2 RNA was monitored by nasal and oropharyngeal (OP) swabs and bronchoalveolar lavage (BAL). Viral RNA was detected in BAL fluid from 2 of the 3 control-immunized macaques on Day 3 after challenge and from 1 of 3, on Day 6. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2 (V9)-immunized and SARS-CoV-2 challenged macaques. The difference in viral RNA detection in BAL fluid between BNT162b2-immunized and control-immunized rhesus macaques after challenge is statistically significant (p=0.0014). From control-immunized macaques, viral RNA was detected in nasal swabs obtained on Days 1, 3, and 6 after SARS-CoV-2 challenge; from BNT162b2 (V9)-immunized macaques, viral RNA was detected only in nasal swabs obtained on Day 1 after challenge and not in swabs obtained on Day 3 or subsequently. The pattern of viral RNA detection from OP swabs was similar to that for nasal swabs. No signs of viral RNA detected vaccine-elicited disease enhancement were observed. The viral RNA levels between control-immunized and BNT162b2-immunized animals after challenge were compared by a non-parametric analysis (Friedman's test), and the p-values are 0.0014 for BAL fluid, 0.2622 for nasal swabs, and 0.0007 for OP swabs.

Despite the presence of viral RNA in BAL fluid from challenged control animals, none of the challenged animals, immunized or control, showed clinical signs of illness (weight change, body temperature change, blood oxygen saturation and heart rate). The Applicant concluded, the absence of clinical signs in any of the challenged animals, immunised or control, despite the presence of viral RNA in BAL fluid from challenged control animals, indicates that the 2-4 year old male rhesus monkey challenge model appears to be an infection model, but not a clinical disease model. However, a further investigation by lung radiograph and computerized tomography (CT) was conducted. Radiographic evidence of pulmonary abnormality was observed in challenged controls but not in unchallenged sentinels nor in challenged BNT162b2-immunized animals except for a CT-score signal in 1 of 6 pre infection and 2 out of six at Day 10/EOP in BNT162b immunised animals. The CT score signal was at the same level as the control at Day 10/EOP. No radiographic evidence of vaccine-elicited enhanced disease was observed.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2, which is acceptable to the CHMP.

Safety pharmacology studies

No safety pharmacology studies were conducted with BNT162b2. The Applicant refers to that they are not considered necessary according to the WHO guideline (WHO, 2005). In addition, no findings on vital organ functions have been recorded in the repeat dose toxicology studies. Thus, the absence of safety pharmacology studies is endorsed by the CHMP.

Pharmacodynamic drug interactions studies

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is agreeable to the CHMP.

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial t½ of 1.62 and 1.72 h, respectively. 24 hours post-dosing, less than 1% of the maximum plasma concentrations remained. A slower clearance rate was observed after 24 hours with ALC-0315 and ALC-0159 terminal elimination t½ of 139 and 72.7 h, respectively.

Following plasma clearance, the liver appears to be to major organ to which ALC-0315 and ALC-0159 distribute. The applicant has estimated the percent of dose distributed to the liver to be ~60% for ALC-0315 and ~20% for ALC-0159. The observed liver distribution is consistent with the observations from the biodistribution study and the repeat-dose toxicology, both using IM administration.

For ALC-0315 (aminolipid), the maximum detected concentration in the liver (294 µg/g liver) was reached 3 hours after IV injection. ALC-0315 was eliminated slowly from the liver and after 2-weeks the concentration of ALC-0315 was still ~25% of the maximum concentration indicating that ALC-0315 would be eliminated from rat liver in approximately 6-weeks. For ALC-0159 (PEG-lipid), the maximum detected concentration in the liver (15.2 µg/g liver) was reached 30 minutes following IV injection. ALC-0159, was eliminated from the liver faster than ALC-0315 and after 2-weeks the concentration of ALC-0159 was only ~0,04% of the maximum detected concentration. The applicant was asked to discuss the long half-life of ALC-0315 and its effect, discussion on the comparison with patisiran, as well as the impact on the boosts and post treatment contraception duration. The applicant considered that there were no non-clinical safety issues based on the repeat dose toxicity studies at doses (on a mg/kg basis) much greater than administered to humans; this was acceptable to the CHMP.

Both patisaran lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives. According to the applicant, it is difficult to further contextualize the pharmacokinetic data and therefore to understand the safety of these molecules, beyond consideration of dose. There is a large dose differential between the human BNT162b2 dose and the dose used in the toxicity studies (300-1000x) which provides an acceptable safety margin.

Moreover, according to the Applicant given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. Finally, the applicant is of the opinion that these results support no requirements for contraception. The CHMP found this position agreeable.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159.

Biodistribution of a LNP-formulated luciferase surrogate reporter:

To determine the biodistribution of the LNP-formulated modRNA, the applicant did study distribution of the modRNA in two different non-GLP studies, in mice and rats, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2 (mouse study) or the biodistribution of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation (rat study).

The mouse study used three female BALB-c mice per group and luciferase protein expression was determined by *in vivo* bioluminescence readouts using an *In Vivo* Imaging System (IVIS) following injection of the luciferase substrate luciferine. The readouts were performed at 6h, 24h, 48h, 72h, 6d and 9d post IM injection (intended clinical route) in the right and left hind leg with each 1 µg (total of 2µg) of LNP-formulated luciferase RNA.

In vivo luciferase expression was detected at different timepoints at the injection sites and in the liver region indicating drainage to the liver. As expected with an mRNA product, the luciferase expression was transient and decreased over time. Luciferase signals at the injection sites, most likely reflecting distribution to the lymph nodes draining the injection sites, peaked 6h post injection with signals of

approximately 10 000 times of buffer control animals. The signal decreased slowly during the first 72 hours and after 6 and 9 days the signals were further weakened to approximately levels of 18 and 7 times the signals obtained from animals injected with buffer control.

The signals from the liver region peaked 6h post injection and decreased to background levels 48h after injection. The liver expression is also supportive of the data from the rat PK study and the findings in the rat repeat-dose toxicological study showing reversible liver vacuolation and increased γGGT levels.

The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.

Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Immunogenicity of a LNP formulated luciferase modRNA:

Activation of the innate immune system following IM injection of a LNP-formulated luciferase reporter RNA into mice was assessed in a Luminex-based multiplex assay were serum samples (day -1 (pre), 6 h and day 9) were tested for levels of the following chemokines and cytokines: MCP-1, MIP-1β, TNF-α, IFN-α, IFN- γ, IL-2, Il-6, IL-10, IL1-β, IP-10. The applicant tested 3 different LNPs, all formulated together with luciferase RNA. The results suggest that the LNP formulation used in BNT162b2 (LNP8) slightly increased levels of MCP-1, IL-6, and IP-10 at 6h post immunisation. All chemokine/cytokine levels dropped to background levels at day 9.

In addition to innate immune activation, LNP formulated luciferase modRNA was able to induce IFN-γ T-cell responses (when challenged with MHC I-specific luciferase peptide pools) measured in splenocytes isolated from the mice at day 9.The LNP formulated luciferase modRNA did not induce the formation of luciferase-specific IgGs as measured by ELISA.

In an additional hPBMC study (R-20-0357), overall, low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. IP-10, MIP-1b, MCP-1 were seen to be increased among donors, because of transfection of antigen presenting cells after infection.

Metabolism of the two novel LNP-excipients ALC-0315 and ALC-0159:

Metabolism studies were conducted to evaluate the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid). No metabolic studies were performed with the modRNA or the other two lipids of the LNP. Overall, it seems as both ALC-0159 and ALC-0315 are metabolised by hydrolytic

metabolism of the amide or ester functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

The metabolism of the novel excipients, ALC-0159 and ALC-0315, were examined *in vitro* using blood, liver S9 fractions and hepatocytes, all from mouse, rat, monkey and human. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver from a rat pharmacokinetics study where a luciferase-encoding modRNA formulated in an LNP was used.

Metabolism of ALC-0315 appears to occur via two sequential ester hydrolysis reactions, first yielding the monoester metabolite followed by the doubly de-esterified metabolite. The monoester metabolite was observed *in vitro* in rat blood, monkey S9 fraction, and *in vivo* in rat plasma and rat liver. The doubly de-esterified metabolite was observed *in vitro* in mouse and rat blood; monkey liver S9 fraction; and *in vivo* in rat plasma, urine, faeces and liver. Subsequent metabolism of the doubly de-esterified metabolite resulted in a glucuronide metabolite which was observed in urine only from the rat pharmacokinetics study. Additionally, 6-hexyldecanoic acid, the acid product of both hydrolysis reactions of ALC-0315, was identified *in vitro* in mouse and rat blood; mouse, rat, monkey and human hepatocytes; mouse, rat and human liver S9 fractions; and *in vivo* in rat plasma.

ALC-0315 was stable over 120 min (>93% remaining) in liver microsomes and S9 fractions and over 240 min (>93% remaining) in hepatocytes in all species and test systems.

The primary route of metabolism for ALC-0159 appears to involve amide bond hydrolysis yielding *N*,*N*-ditetradecylamine. This metabolite was identified in mouse and rat blood as well as hepatocytes and liver S9 from mouse, rat, monkey and human.

ALC-0159 was stable over 120 min (>82% remaining) in liver microsomes and S9 fractions and over 240 min (>87% remaining) in hepatocytes in all species and test systems.

Excretion of the two novel LNP-excipients ALC-0315 and ALC-0159:

Excretion of the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) was studied in the rat PK study. No excretion studies were performed with the modRNA or the other two lipids of the LNP which is considered acceptable by the CHMP.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Since almost no unchanged ALC-3015 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.3.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies and one DART fertility-EFD rat study. The test substance in the repeat-dose toxicity studies is BNT162b2 (100 µg of variant 8 in one study (study 38166) and 30 µg of the clinically relevant variant 9 in the second study (study 20GR142)), which consists of a modified RNA in a lipid nanoparticle (LNP) formulation. The differences between the variants are due to codon optimization. The LNP contains four excipients whereof two are considered novel (ALC-0315 and ALC-0159).

Repeat dose toxicity

The two general/repeat-dose toxicity studies involved IM exposure of Han Wistar rats to BNT162b2 for a total of 17 days (three weekly administrations) followed by three weeks of recovery. Overall, the

study designs only included a single experimental group each with a variant of BNT162b2 (V8 or V9 variant), with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. No test substance-linked mortality or clinical signs were observed (except a slight increase [<1C] in body temperature). No ophthalmological and auditory effects were found. The animal model of choice, the rat, has not been assessed in the pharmacological dossier but a limited absorption/distribution study has been conducted in pharmacokinetics dossier. Immunogenicity was assessed in the toxicology studies.

Body weight and food intake: Exposure generated a slight reduction of absolute BW statistically significant at D9 (-6.8% to -11.3%; BNT162b2 V8) alternatively a weak body weight increase reduction [BNT162b2 v9]. No changes in food intake were observed.

Gross pathology and organ weights: At 100ug BNT162b2 V8 and 30ug BNT162b2 V9, the tissue at the injection site was thickened/enlarged with oedema and erythema at the end of exposure in a reversible manner. The spleen was enlarged (reversible) with up to 60% for both vaccine variants and doses. There was also an enlargement of the draining and inguinal lymph nodes at 100ug (BNT162b2 V8). Overall, there were signs of a significant immune response which is likely linked to the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8) but not at 30ug (BNT162b2 V9).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis inflammation and epidermis hyperplasia). Also, there was inflammation of the perineural tissue of the sciatic nerve and surrounding bone in most rats at d17. The bone marrow demonstrated increased cellularity and the lymph nodes showed plasmacytosis, inflammation and increased cellularity. The spleen demonstrated increased haematopoiesis in half the animals at d17. The liver showed hepatocellular periportal vacuolation at d17 (fully reversed during recovery) which may be related to hepatic clearance of ALC0315. Histopathology assessment of 30ug BNT162b2 V9 generated similar results as 100ug BNT162b2 V8 although not on as extensive level (possibly due to a lesser dose). Minimal to moderate inflammation and oedema was observed at the injection site (usually resolved after ~3d). There was minimal to moderate increased plasma cell cellularity in the lymph nodes and germinal center cellularity plus hematopoietic cell cellularity in the spleen at d17 (reversible at end of recovery). There was minimal increase cellularity in the bone marrow. Reversible vacuolisation in the liver was also observed.

The Applicant explained that peri-portal liver vacuolization was observed in both pivotal studies but are not related to any microscopic evidence of liver/biliary injury in animals (cellular hypertrophy, inflammation) nor any clinical data from Phase 1 study. Vacuoles are considered by the Applicant to be a result of ALC-0315 accumulation in liver and not PEG.

A novel finding at 30ug was minimal extra-capsular inflammation in the joints at d17.

Moreover, increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells does not provide additional information. The CHMP found this agreeable.

Immunogenicity: Treatment of rats with 100 ug BNT162b2 V8 generated SARS-CoV-2 neutralizing titers (based on a vesicular stomatitis virus (VSV)-based pseudovirus neutralization assay) and IgG antibodies against the S1 fragment and the RBD (based on ELISA) in serum samples. Treatment of

rats with 30 ug BNT162b2 V9 generated SARS-CoV-2 neutralizing antibodies (not a pseudovirus neutralization assay).

Haematology: At 30ug BNT162b2 V9 and 100ug BNT162b2 V8, there was a moderate to strong reduction of reticulocytes (48-74%, not specified for V9) coupled to lowered red cell mass parameters (RBC, HGB, and HCT). There was a moderate to strong increase (>100%) in large unclassified cells [LUC], neutrophils, eosinophils, basophils and fibrinogen that may be related to the inflammatory/immune response. The changes were reversible. No effects on coagulation were observed for V8 whereas a slight increase in fibrinogen was observed with V8 and V9.

Clinical pathology: A very strong but reversible increase (>100%) in pro-inflammatory acute phase proteins in the blood (A1AGP, A2M) was seen with both 30ug BNT162b2 V9 and 100ug BNT162b2 V8. Also, indicative of pro-inflammation, a slight to moderate reduced albumin/globulin ratio was seen for both variants. V8 (100ug) exposure generated increased levels of γGT (>200%) and increased γGT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate increases in AST and ALP levels (+20-100%), possible indicative of liver effects but no changes in γGT levels. There were no changes in cytokine levels (IFNγ, TNFalpha, Il-1b, Il6, Il-10) after 100ug V8 exposure (not measured for V9). For 100ug V8, there were no changes measured in urine whereas there was a slight-moderate reduction in pH for 30ug V9.

Genotoxicity

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

Reproduction Toxicity

In the DART study, the test substances used were BNT162b1, BNT162b2 and BNT162b3, which were given to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). The test substances were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 doses. A subgroup was terminated at GD21 and another (litter) group was terminated at PND21. SARS-CoV-2 neutralizing antibody titers were found in the majority of females just prior to mating (M-14), in most females and foetuses at the end of gestation (GD21), and in most offspring at the end of lactation (PND21). There was transient reduced body weight gain and food consumption after each dose. No effects on the estrous cycle or fertility index were observed. There was an increase (~2x) of pre-implantation loss (9.77%, compared to control 4.09%) although this was within historical control data range (5.1%-11.5%). Among foetuses (from a total of n=21 dams/litters), there was a very low incidence of gastroschisis, mouth/jaw malformations, right sided aortic arch, and cervical vertebrae abnormalities, although these findings were within historical control data. Regarding skeletal findings, the exposed group had comparable to control group levels of presacral vertebral arches supernumerary lumbar ribs, supernumerary lumbar short ribs, caudal vertebrae number < 5). There were no signs of adverse effects on the postnatal

pups (terminated at PND21). It is noted that there is currently no available data on the placental transfer of BNT162b2. This information is reflected in section 5.3 of the SmPC.

Local Tolerance

No dedicated local tolerance studies have been conducted; however the assessment of local tolerance was performed in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly slight to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The data for 30ug BNT162b2 V9 exposure indicated less severe but similar effects.

2.3.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The proposed medicinal product is composed of a modRNA formulated with functional and structural lipids forming lipid nano particles (LNPs), the latter having the purpose to protect the modRNA from degradation and enable transfection of the modRNA into host cells after IM injection. The composition of the LNPs is likely to affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity (see also toxicology below).

The general immune activating mode of action of LNP-formulated RNA vaccines have been described in the literature. The administration of LNP-formulated RNA results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Whether other cells than professional APCs may transiently express the vaccine derived spike protein and therefore from a theoretical point of view, as compared to SARS-CoV-2 infected cells, also could potentially be targets for previously primed spike protein reactive cytotoxic T cells, if present, is not known. However, no overt signs of such adverse pharmacological responses have been recorded in the repeat dose toxicity study or in the clinical trials. In the clinical trial, a second dose was administered to patients who had been immunologically primed by the first dose. Moreover, in the clinical trials it appeared around 270 patients that was shown to have been seropositive for SARS-COV-2 before vaccination. In these cases, the expression of the spike protein on host cells occurred in the presence of a primed immune response to the spike protein but no overt adverse pharmacological response has been observed. The low amount of vaccine product in a single dose may limit the distribution of modRNA/LNP mainly to the injection site and to migrating APCs. Due to the transient expression of the modRNA, no persistent expression is expected.

Regarding the structural and biophysical characterization of the modRNA, a schematic description shows that 5 different sequences are included in the BNT162b2, of which two being coding sequences.

Concerning the protein expression obtained from the V8 and V9 variants, specific immune responses (total IgG binding Ab + neutralizing Ab) were obtained at significant levels against the Spike S protein in animals with both variants (in mice and rats), indicating the efficiency of the *in vivo* expression of Spike S protein. An additional study was provided (R-20-0360) further demonstrating *in vitro* protein expression. Transfection efficiency, expression rate and cellular viability were analysed in HEK293T cells, upon transfection with different constructs (saRNA, uRNA, modRNA V8 and V9). HEK293T cells were efficiently transfected by both modRNA V8 and modRNA V9 with higher transfection rate for V9, but quite similar the expression rate by V8 and V9.

Although some of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided, it was investigated in supportive studies based on P2S expressed from DNA and not the product modRNA. While it is not considered to be of critical importance for the assessment in this procedure, it still provides a scientific understanding supporting the nonclinical key studies of humoral and cellular immune response, including SARS-CoV-2 neutralizing antibodies, as well as SARS-CoV-2 challenge nonclinical PoC.

In-vivo pharmacodynamics: The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates and was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Nonhuman primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. This is accepted but a more in-depth discussion on the suitability of these pharmacological animal models have not been provided (e.g. susceptibility for SARS-CoV-2 infection and similarity to COVID 19 disease; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains). Only single immunisation was conducted in mice, as compared to the clinical 2-dose regimen, which was adequate since only characterization of the immune response, but no challenge study was carried out in mice. Also, no or limited attention to the induction of long-term memory responses nor immunogenicity and protection in aged animals has been paid. That being said, the induction of virus neutralizing antibodies in both mice (VSV-SARS-CoV-2 S) and primates (SARS-CoV-2) indicated that BNT162b2 immunization has the potential to induce neutralizing antibodies also in humans. Thus, vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity.

In mice, the immune response was assessed by single immunization only. Taking the phenotyping of B and T cells in aggregate, the data indicates a concurrent induction of SARS-CoV-2 S-specific neutralizing antibody titers and a Th1-driven T-cell response by immunization with BNT162b2 (this was also seen in nonhuman primates).

Concerning the nonhuman primate (rhesus macaques) studies, the applicant considers the human convalescent serum panel as an assessable benchmark to judge the quality of the immune response to the vaccine; this is accepted by the CHMP.

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFNγ producing T cell responses, including a high frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-α but a low frequency of CD4+ cells that produce IL-4, indicates a Th1-biased response occurred after the BNT162b2 (V9) immunization. This reasoning appears acceptable to the CHMP. The role of such a Th1 biased response was put in the context of antigen-specific T-cell responses playing an important role in generation of antigen-specific antibody response as well as in elimination of infected cells to mediate protection against disease.

When immunised macaques were challenged with SARS-CoV-2, a clear and statistically significant effect was observed on reduced presence of viral RNA in bronchoalveolar lavage (BAL) and oropharyngeal (OP) swabs. A clear effect was also recorded by blinded X ray scoring of the lungs. A

protective effect is also evident in the CT score Day 3 after challenge, however at Day 10/EOP, there was a CT signal in 2 out of six BNT162b immunized monkeys at the same level as observed in the control group. That signal is of unclear significance since also in 1 out of 6 pre infection BNT162b immunized animals a similar CT-score signal was observed. During this time period the SARS-CoV-2 neutralizing GMT in the BNT162b2-immunised rhesus macaques continued to decrease but remained above the GMT of a human convalescent serum panel.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing antibodies and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters, provide support for the vaccination approach. Due to species differences in the immune system between animal model species and humans, the conclusion whether this candidate vaccine will be sufficiently effective in humans needs to be established in clinical studies.

Pharmacokinetic

Pharmacokinetic (regarding the two novel LNP excipients): The two novel lipid excipients play different roles in the formulation and have different pharmacokinetics. It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0315.

ALC-0159 is comprised of a polyethylene glycol (PEG) headgroup (~2000 M.Wt.) attached to hydrophobic carbon chains (ie, the lipid anchor). ALC-0159 is present in BNT162 at a low mol% (<2 mol%), and therefore dose, relative to the other lipids. PEGylated lipid can exchange out of the LNP after administration, thus allowing the desired binding of endogenous proteins (eg, Apolipoprotein E) and removing the steric barrier that would otherwise restrict interactions of the LNP with target cells and proteins.

ALC-0315 is an ionizable aminolipid in BNT162b2 and is the most important lipid component for efficient self-assembly and encapsulation of the mRNA within the LNP, and for providing successful delivery of mRNA into target cells.

The PEG-lipid (ALC-0159) is designed to largely exchange out of the LNP after administration and before uptake into target cells, whereas the aminolipid (ALC-0315) is critical to the efficient intracellular delivery of the mRNA through endosomal uptake and release and must remain with the LNP.

ALC-0159 is much more hydrophilic, in large part due to the presence of the PEG molecule which is known to be a strongly hydrophilic molecule (Ma et al, 1990). Due to the more hydrophilic and essential neutral nature of this molecule, ALC-0159 has a much lower affinity for tissues and relative to ALC-0315 there will be freer compound available for redistribution from tissue to plasma; thus, elimination will be more rapid.

The Applicant pointed out that during the course of the 2-week pharmacokinetic study, liver concentrations of ALC-0315 fell 4-fold from their maximum value indicating that 75% of the material delivered to the liver was eliminated over this two-week period.

ALC-0315 has no known biology. In the absence of this 'biological relevance' the applicant used an estimation of >95% elimination of ALC-0315 to represent the essential elimination from the body. The elimination half-life of ALC-0315 in the liver following IV administration in the rat is approximately 6-8 days. These data indicate that 95% elimination of ALC-0315 will occur approx. 30-40 days following final administration in the rat.

Based on the understanding of the process involved in the terminal half-life, redistribution from tissues into which the lipid nanoparticle is delivered, a similar half-life and time to 95% elimination in human is expected (Mahmood et al, 2010). Examination of the scaling of the comparable lipids (PEG2000-C-DMG, DLin-MC3-DMA) in patisiran indicates that the half-life of these lipids appears to scale with a value approaching the typically used exponent for half-life (0.25). If this is the case for ALC-0315 we may

expect a half-life approximating 20-30 days in human for ALC-0315 and 4-5 months for 95% elimination of the lipid (Mahmood et al, 2010).

Both lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives.

Given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. This is noted by the CHMP.

Biodistribution: Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain.

In line with this, results from the newly transmitted study 185350, indicate a broader biodistribution pattern with low and measurable radioactivity in the ovaries and testes. Given the current absence of toxicity in the DART data, the absence of toxicological findings in gonads in the repeat-dose studies and that the radioactivity in the gonads were low (below 0,1% of total dose), the current data does not indicate it to be a safety concern. The relative high dose used in the rats (500x margin to human dose based on weight) also supports a low risk from distribution to the gonads in humans.

RNA stability and kinetics are not expected to be the same for all RNAs and are influenced by the nucleosides of the RNA and although expression of the full-length spike (S) protein is expected to follow similar kinetics of that of the luciferase with a transient expression fading over time, it cannot be excluded that differences in stability/persistence of the signal could differ between the luciferase protein and the spike (S) protein.

In an additional hPBMC study (R-20-0357), low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. The Applicant underlines that no specific general trend in cytokine secretion can be observed, given variability among donors and based on the low numbers of donors in the experiment.

Toxicology

Although no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate), the rat was used as a toxicological animal model in the repeat-dose toxicity studies. The positive neutralization assay results in the repeat-dose toxicity studies demonstrate that V8 and V9 generate an immune response in this species (i.e. SARS-CoV-2 antibodies), partially supporting the use of the rat as an animal model. Other SARS-CoV-2 immune responses in rat remain unclear. The immune responses, especially at the injection sites (e.g. oedema, erythema), seem to increase with each injection in the studies (n=3). There was a marked increase in acute phase proteins, fibrinogen and reduced albumin-globulin ratio (but no increase in cytokines with V8, unclear for V9). There was also a general increase in immune cells (LUC, neutrophils, eosinophils, basophils) and a decrease in red blood cell parameters (reticulocytes, RGB, HGB, HCT). The spleen was enlarged at both 30ug V9 and 100ug V9 and the draining and inguinal lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30ug (V9).

Systemic complement activation (which sometimes may be induced by liposomal drugs and biologicals and potentially result in hypersensitivity reactions) was not investigated as no signs indicative of such clinical manifestations were detected. An absence of dose-response designs in the studies increases the difficulty to interpret the effects. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. Increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the

inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The Applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells would not provide additional information. The CHMP agreed with this position.

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

As the pharmacokinetic distribution studies in rat demonstrated that a relatively large proportion - second to the levels at the injection site - of the total dose distributes to the liver (up to 18%, and far more than levels seen in spleen [<1.1%], adrenal glands [<0.1%] and ovaries [<0.1%]). While there was no severe pathogenesis in liver, there were some reversible functional hepatic and/or biliary effects with V8 and V9 (enlarged liver, vacuolation, strongly increased γGT levels at >200% and activity, minor-moderate increase in levels of AST and ALP) which may be linked to the LNP. The γGT changes were not observed with 30ug V9, which may be due to variant differences and/or, more likely, a lower dose. The applicant is of the view that the vacuoles are a result of primarily ALC-0315 accumulation in liver. It can be noted that ALC-0159 needs to be lost from the surface of the LNP to facilitate efficient uptake into target cells. At the same time, ALC-0315 is present in the LNP at a high mol% (50 mol%) relative to the other lipids in the BNT162 vaccine, suggesting that this lipid is more likely to be present within the cells (and possibly in the vacuoles).

The assessment of the data available as regards to the DART study shows that there is no clear adverse signs on fertility and early embryogenesis effects. There were no effects on the oestrous cycle in dams but there was an ~2x increase in pre-implantation loss (~9.77% vs 4.1% in controls) but these effects are within historical control data (5.1% to 11.5%) so these findings do not raise any specific concern. It can be noted that the choice of rat as an DART animal model is supported by means of the repeat-dose toxicity rat studies which demonstrates an immune response to the vaccine candidates [V8 and V9] and the publication of Bowman et al (2013; PUBMED ID [PMID] 24391099) that reports that foetal-maternal IgG ratios are relatively low during organogenesis but that these ratios approach 1 by the end of gestation in both rat and human.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed other concerns raised to be granted MA from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

Some rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher exposure in rats due to body weight differences) developed some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) which is consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible. These findings are described in SmPC section 5.3.

As per guidance, no genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential. This is acceptable to the CHMP.

Finally, the combined fertility and developmental toxicity study showed that SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, gestation, or embryo-foetal or offspring development up to weaning. The CHMP noted that no data are available on vaccine placental transfer or excretion in milk.

2.4. Clinical aspects

2.4.1. Introduction

Pfizer and BioNTech have developed a vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application. Multiple vaccine candidates are being evaluated in this study. For each vaccine candidate, participants received escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pivotal study for registration. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

GCP

The Applicant claimed that the Clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic, EMA gathered additional information as indicated below from EU and non-EU regulatory authorities, and shared them with the CHMP to be considered in the assessment:

- a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;
- Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);
- A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 162-02).

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

- Tabular overview of clinical studies

Table 1 Overview of the Clinical Development

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

Table 2 Overview of the pivotal phase 3 study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
C4591001	131 United States 9 Turkey 6 Germany 4 South Africa 2 Brazil 1 Argentina.	randomized, multinational, placebo-controlled, observer-blind,	2 doses of 30 µg given 21 days apart	Primary: To evaluate the efficacy of BNT162b2 against confirmed severe COVID-19 occurring from 7 and 14 days after the 2nd dose in participants with and without evidence of infection before vaccination	Healthy volunteers at risk of COVID-19	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

For vaccines, pharmacodynamics relates to investigation of immunogenicity. The available data were generated from the phase 1/2 study BNT162-01 conducted in Germany, and from the phase 1 and 2 parts of the phase 1/2/3 study C4591001, conducted in the USA (later phases were multinational). Both studies were designed to choose the optimal vaccine candidate and an appropriate dose and schedule for further studies. Among the four prophylactic SARS-CoV-2 RNA vaccines initially tested the following two candidates were selected for further development:

BNT162b1: RNA-lipid nanoparticle (LNP) vaccine containing nucleoside-modified messenger ribonucleic acid (modRNA) that encodes the RBD (receptor-binding domain)

BNT162b2: RNA-LNP vaccine containing modRNA that encodes SARS-CoV-2 full-length, P2 mutant (see section 2.2.2), prefusion spike glycoprotein (P2 S).

Key features of the two studies are summarised in the below table.

Study id	BNT162-01	C4591001
Title	A multi-site, Phase 1/2, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using	A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine

	different dosing regimens in healthy adults	Candidates Against COVID-19 in Healthy Individuals
Design	This is an open-label, multi-site, Phase 1/2, 2-part, dose-escalation study. Part A of the study includes the first in human dose and dose ranging groups in healthy adults (aged 18 to 85yrs).	This is a Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s); and Phase 2/3 as an expanded cohort and efficacy part.
Immunogenicity objectives	To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titre	To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses
Study population	Healthy adults aged 18 to 55yrs BNT162b1: N=84 (12/group) BNT162b2: N=60 (12/group) Healthy adults aged 56-85 yrs BNT162b1: N=36 (12/group) BNT162b2: N=36 (12/group)	Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive Phase 1 comprised 15 participants (randomization ratio of 4:1 so that 12 received active vaccine and 3 received placebo) per group; 13 vaccine groups were studied, corresponding to a total of 195 participants (the 100 µg dose was only used in the younger adult cohort)
IMP and dose level	BNT162b1: 1µg, 3µg, 10µg, 20µg, 30µg, 50µg, and 60µg. BNT162b2: 1µg, 3µg, 10µg, 20µg, 30µg	BNT162b1: 10 µg, 20 µg, 30µg, 100 µg BNT162b2: 10µg, 20µg, 30µg Placebo: normal saline
Dosing frequency	Two injections ~21d apart	Two injections ~21d apart
Immunogenicity endpoints	Virus neutralization test (VNT). Antibody binding assay, CMI assays, e.g. ELISpot and intracellular cytokine staining (ICS).	SARS-CoV-2 neutralization assay S1-binding IgG level assay RBD-binding IgG level assay N- binding antibody assay

Endpoints and Assays used to evaluate immunogenicity

In Study BNT162-01, immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine neutralizing titres and the fold rise in SARS-CoV-2 serum neutralizing titres. Immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1 (Day 8); and at Day 22 (before Dose 2) and 7 days, 14 days, and 21 days after Dose 2. Only qualified assays were used. In addition, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from

whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immuno-spot (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS). Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFNγ and IL-2 and those associated with Th2 responses such as IL-4, to analyse the induction of balanced versus Th1-dominant or Th2-dominant immune responses.

In Study C4591001, immunogenicity was evaluated in Phase 1 and Phase 2 using a SARS-CoV-2 serum neutralization assay to determine titres and a SARS-CoV-2 RBD- or S1-binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were assessed also. Only qualified assays were used. In Phase 1, immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1; and at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarized for each dose level and age group. In Phase 2, immunogenicity was assessed at Day 1 (before Dose 1) and 1 month after Dose 2. Data were summarized for each age strata group and by evidence of prior SARS-CoV-2 infection at baseline per NAAT (PCR) or N-binding IgG assay. To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

These are the immunogenicity assays that were used in clinical trials:

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 S1-binding IgG in Human Serum

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 RBD-binding IgG in Human Serum

Roche Elecsys SARS-CoV-2 N Binding Antibody Assay

mNeonGreen SARS-CoV-2 Microneutralization Assay

ELISpot Assay

Intracellular Cytokine Staining (ICS) for BNT162b1 and BNT162b2

The SARS-CoV-2 Wuhan-Hu-1 isolate spike glycoprotein (GenBank accession # QHD43416.1) is the reference sequence for the recombinant S1 and RBD proteins used in the Luminex assays. The SARS-CoV-2 neutralisation assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020).

Study BNT162-01

Immunogenicity - functional antibody responses (secondary objectives)

Functional antibody titre data are available up until Day 43 for younger adults (18 to 55 yrs) dosed with 1, 10, 30, 50, and 60 µg BNT162b1 on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group). Data are available for the 10 and 30 µg up until Day 50 for younger adults dosed with 1, 10, 20, and 30 µg BNT162b2 on Days 1 and 22 (dose level 1 µg, n=9; dose levels 10, 20, and 30 µg, n=12).

Virus neutralizing antibody GMTs for participants aged 18 to 55 years after dosing with BNT162b1, are shown in Figure 3. On Day 22, at 21 d after the first dose, virus neutralizing antibody GMTs had increased in a dose-dependent manner for all dose groups. At 7 d after the second dose (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 µg dose group,

which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titres.

On Day 43 (21 d after the second dose of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs at least 14 d after confirmed diagnosis and at a time when the individuals were asymptomatic.

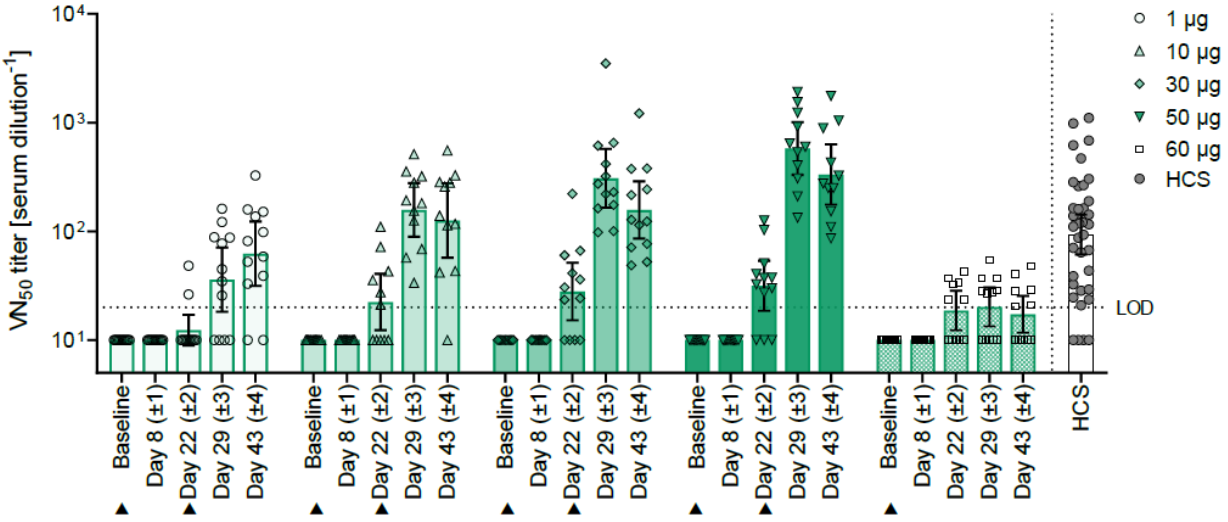


Figure 3: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN50) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 years) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum

For virus neutralizing antibody GMTs for participants aged 18 to 55 yrs after dosing with BNT162b2, see Figure 4. Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger participants (aged 18 to 55 yrs) immunized with ≥3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult in the 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

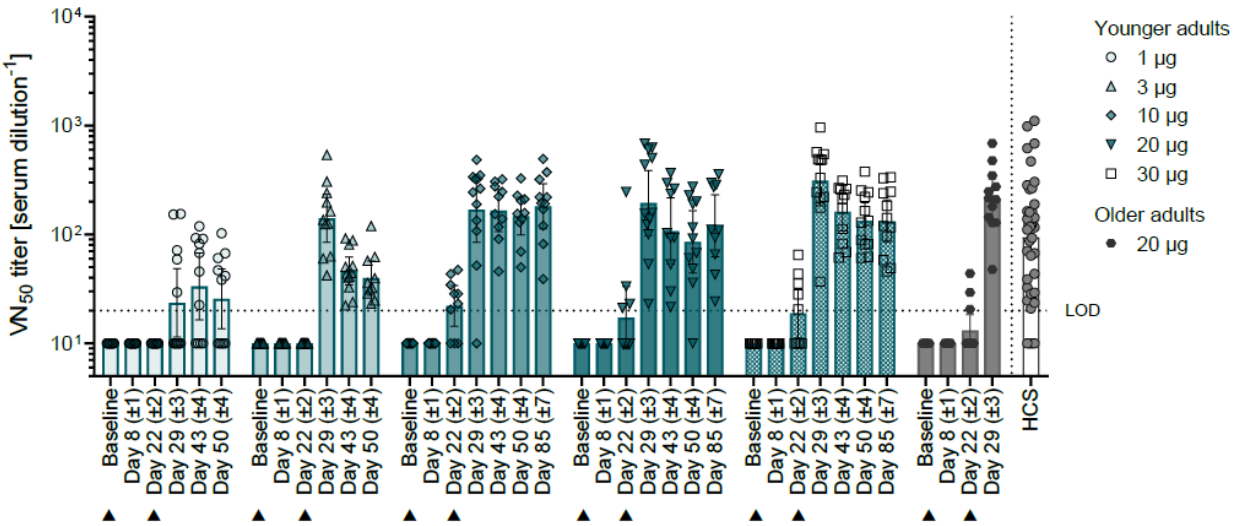
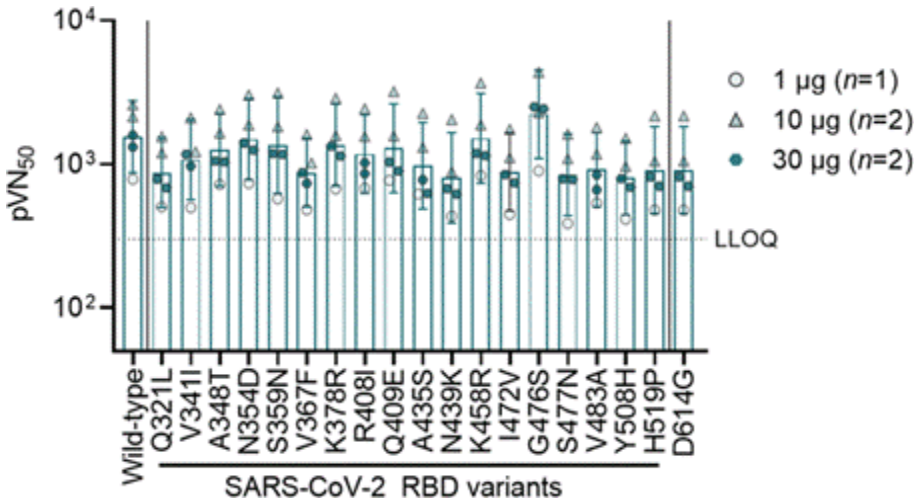


Figure 4: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titres (VN50) – IMM
VN50 titres with 95% confidence intervals are shown for younger adults (aged 18 to 55 years) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD.
IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum.

Neutralisation of different spike protein mutants

Different pseudoviruses including RBD sequence variants have been tested in a pseudovirus neutralization assay with sera from BNT162b1-and BNT162b2-immunized participants in the BNT162-01 study. Efficient neutralization of spike protein mutants was observed with sera from BNT162b1- and BNT162b2-immunized participants demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies.



BNT162b2-induced virus neutralization titers with pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel with 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G. LLOQ = Lower level of quantification (at 300). Data shown as group (total n=5) GMT with 95% CI.

Cell mediated immunity (CMI)

CMI were measured in terms of IFNγ- producing CD4+ and CD8+ T cells by ELISpot. Both vaccine candidates elicited clear responses (baseline vs post-dose 2). Further characterisation was determined using intracellular cytokine staining for Th1 cytokines (IFNγ, IL-2) and Th2 cytokines (IL-4). Both vaccine candidates stimulated predominantly Th1 responses, both in CD4 and CD8 T cells.

Study C4591001

Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations. Phase 1 and Phase 2 data were reported as the following, for SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-binding and RBD-binding IgG concentrations:

- geometric mean titers/concentrations (GMTs/GMCs)
- geometric mean-fold rise (GMFR)
- geometric mean ratio (GMR) (for Phase 1 only)
- proportions of participants with ≥4-fold rise (for Phase 1 only)
- antibody titers/levels at defined thresholds (for Phase 2 only)

For immunogenicity results of SARS-CoV-2 serum neutralizing titers and S1- or RBD-binding IgG concentrations, GMTs or GMCs were computed with associated 95% CIs.

The GMFR was calculated by exponentiating the mean of the difference of logarithm transformed assay results: (later time point) – (earlier time point) with two-sided CIs. The GMR was calculated as the mean of the difference of logarithm transformed assay results: (SARS-CoV-2 serum neutralizing titers) – (SARS-CoV-2 anti-S binding antibody) for each participant, then exponentiating the mean, with two-sided CIs.

Results

The study set out to evaluate 2 SARS-CoV-2 RNA vaccine candidates, as a 2-dose (separated by 21 days) schedule, at different dose levels (BNT162b1: 10, 20, 30, and 100 µg, BNT162b2: 10, 20, and 30 µg) and in different age groups (18 55 y; 65-85 y), to select a vaccine and dose level for further testing in Phase 2/3. Cut-off date: 24-Aug-2020 (1 month post-dose 2 = D52).

Immunogenicity results are available for both adult age groups up to 1 month post-Dose 2 for the BNT162b1 and BNT162b2 vaccine candidates at the 10-µg, 20-µg, and 30-µg dose levels, and up to 7 weeks after Dose 1 of BNT162b1 at the 100-µg dose level (younger age group only).

Results for the 7 days after Dose 1 time point are only analysed and presented in the younger age group (18 to 55 years of age) for 10 µg and 30 µg BNT162b1.

Immunogenicity results SARS-CoV-2 Neutralizing Titres

BNT162b1

In the younger age group, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b1 (Figure 5).

Generally similar trends were observed in the older age group, with higher GMTs observed in the 20-µg and 30-µg dose groups of BNT162b1 compared to the 10-µg dose group (Figure 6). In the older age

group, the SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.

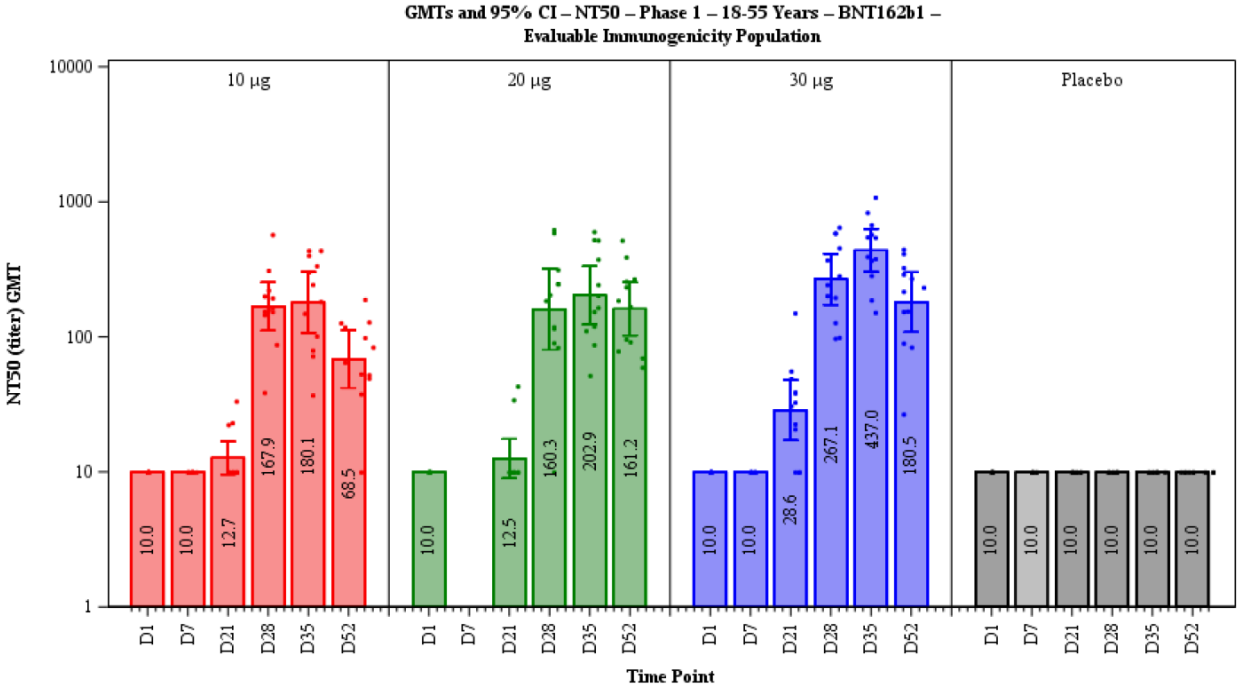


Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

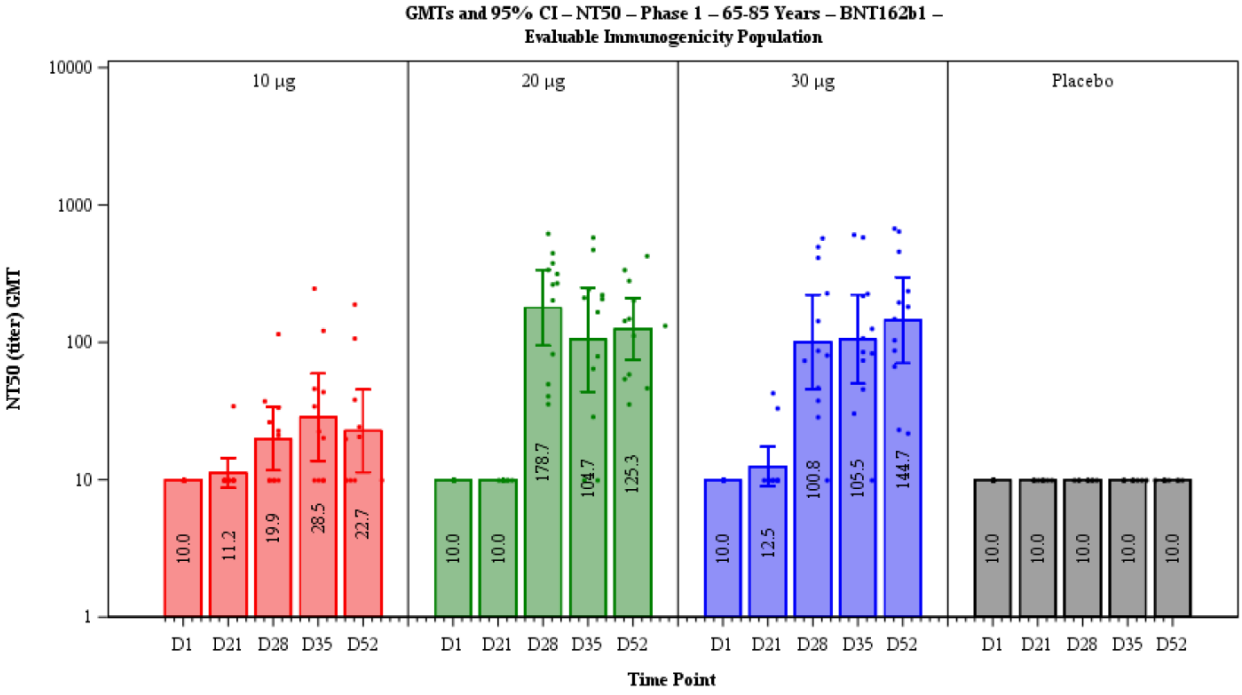
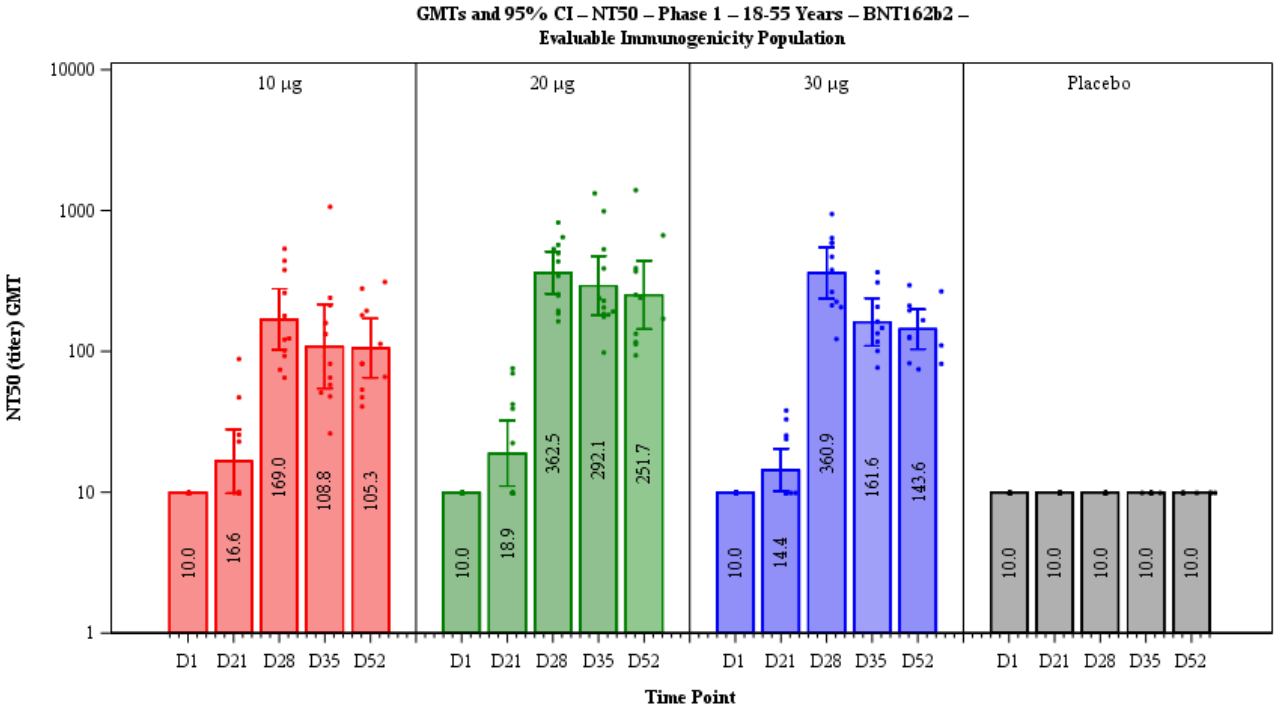


Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart– 65-85 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

BNT162b2

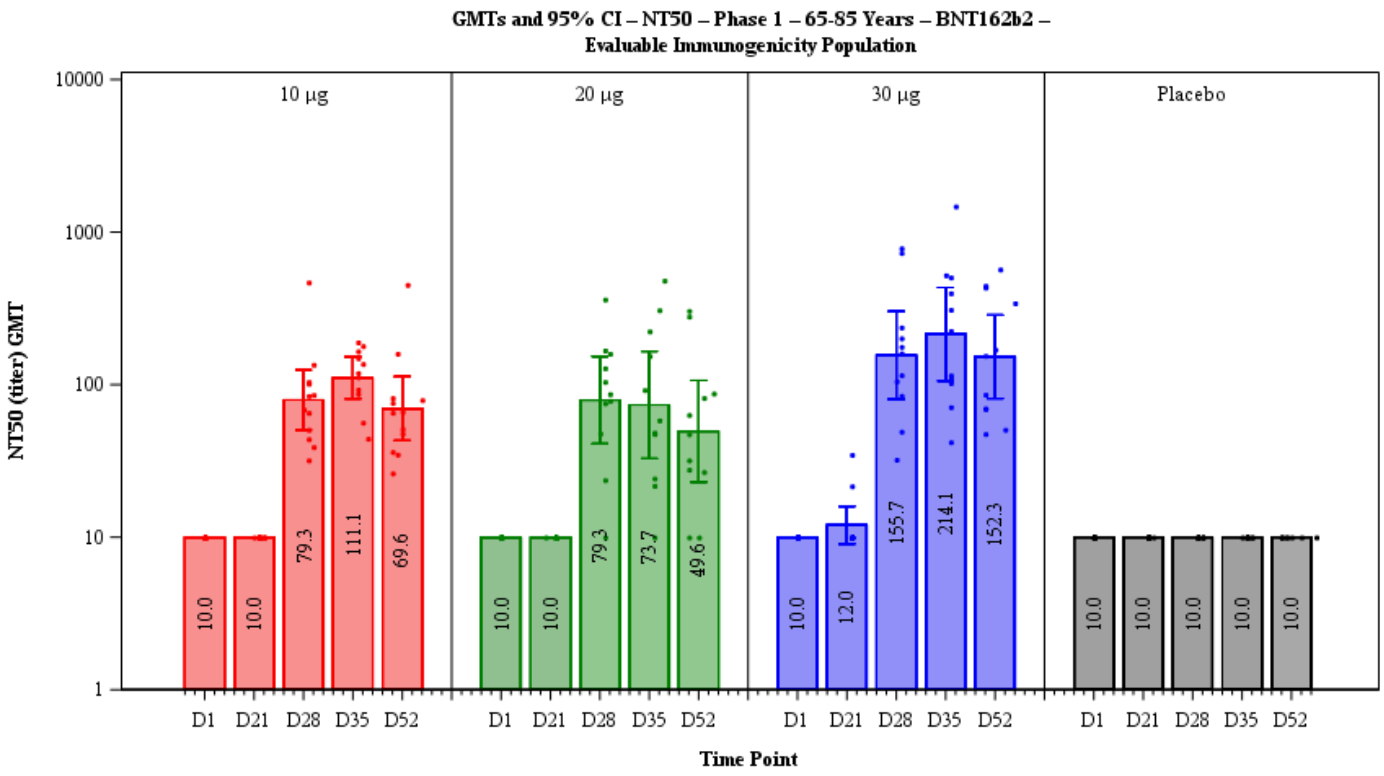
In the younger age group, SARS-CoV-2 50% neutralizing GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2 (Figure 7).

Similar trends were generally observed in the older age group, with higher GMTs observed in the 30-µg dose groups compared to the 20-µg and 10-µg dose groups (Figure 8). In the older age group, SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

Figure 8. Geometric Mean Titres and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

2.4.4. Discussion on clinical pharmacology

The choice and dose of vaccine candidate was based on the results of two clinical phase I studies. Immune responses and safety of the two candidates were studied in both studies. The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first dose. Thus, in the absence of a serological correlate of protection, these data supported that two doses would be needed in adults. The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10ug and 30ug. The neutralising antibody responses between the two vaccine candidates are considered similar although no formal comparison was made. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001. In both studies subjects 55 years of age and older were included as well as younger adults. The responses in elderly were lower compared to younger adults, but the difference is likely of no clinical relevance, also considering the delayed peak.

For BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable to the kinetics of neutralizing antibodies, with lower IgG concentrations in older age group than in younger age group.

Further evaluation of antibody persistence is ongoing. Neutralizing antibody titres will be followed until the end of 162 days post-dose 2 for study BNT162-01 and up to 2-years for study C459001. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation).

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will be also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralization of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunized study BNT162-01 participants, demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies. This may be important to consider when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

Further characterisation of immune responses was included in study BNT162-001. Cellular immune responses were demonstrated in terms of IFNγ-producing CD4 and CD8 T cells. In addition, a clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 µg dose cohort vaccinated with BNT162b1, RBD-specific IL-2 producing CD4+ and CD8+ T cells were reduced in older adults.

2.4.5. Conclusions on clinical pharmacology

The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 µg. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation), including data on persistence of immune responses.

2.5. Clinical efficacy

2.5.1. Dose response study

See section 2.4.3.

2.5.2. Main study

Title of study

Study C4951001: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Methods

Study Participants

Main Inclusion criteria:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3) at randomization.
- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks

before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.

- Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent

Exclusion criteria:

- Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation
- Previous participation in other studies involving study intervention containing lipid nanoparticles.

Treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 µg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Available safety, efficacy and immunogenicity data pertain to vaccine made according with the manufacturing process employed for clinical trial batches.

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (commercial process) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. Data are expected in February 2021. See the Quality section regarding comparability of clinical lots and commercial lots.

Objectives

The outcomes of the primary efficacy objectives were included in the Clinical Study Report submitted in this application. Results of the secondary objectives are expected during 2021.

Primary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination

Primary safety objectives

- To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)
- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3

Secondary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

Secondary immunogenicity objectives

- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (data not included in this report)

Exploratory objectives

- To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination
- To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study
- To describe the serological responses to the BNT vaccine candidate in cases of:
  - Confirmed COVID-19
  - Confirmed severe COVID-19
  - SARS-CoV-2 infection without confirmed COVID-19
- To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease
- To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

Outcomes/endpoints

Immunogenicity

See pharmacodynamics section for description of immunological methods used in phase 1 and 2 of this study. The same methods are used also in phase 3, but results are not yet available.

Primary Efficacy Endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Secondary Efficacy Endpoints

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2.

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

COVID-19 Case Definitions

Participants who developed any potential COVID-19 symptoms were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (within 3 days of symptom onset and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a self-swab was used), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis. Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was only acceptable if it met protocol specified criteria and if a central laboratory result was not available.

Two definitions of SARS-CoV-2 related cases, and SARS-CoV-2 related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

Confirmed COVID-19 (defined for FDA guidance): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhoea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2<300mm Hg);

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

In addition, evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen. A serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

In addition, prior infection with SARS-CoV-2 was assessed also at Dose 2 (NAAT) and is being evaluated for up to 24 months. The purpose is to assess persistence of efficacy, explore efficacy against asymptomatic SARS-CoV-2 infections, and ensure safety in both seronegative and seropositive participants.

Sample size

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

Randomisation and Blinding (masking)

Allocation of participants to vaccine groups were performed through the use of an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants ≥12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

Exceptions to blinding for e.g. DMC activities were described and found acceptable.

Efficacy Analysis Methods

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (i.e., Pr[VE >30%|data] >99.5% at an interim analysis or >98.6% at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating vaccine efficacy at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated. VE is defined as 100% × (1 – IRR), where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (i.e., posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2.

The interim analysis was performed for the first primary efficacy endpoint only. Other efficacy data analysed for the interim analysis were summarized with descriptive summary statistics, including COVID-19 case counts in the BNT162b2 and placebo groups on the basis of:

- evidence of prior SARS-CoV-2 infection at baseline per NAAT or N-antigen binding assay
- subgroup status (i.e., age, sex, race, ethnicity baseline SARS-CoV-2 status)
- COVID-19 cases meeting protocol criteria as severe after the first and second doses.

Overwhelming efficacy success criteria were met at the first interim analysis, so further formal interim analyses would not be conducted. The final analysis of all protocol specified primary and secondary efficacy endpoints was pre-specified in the protocol to be conducted after accrual of the final number of COVID-19 cases (at least 164 cases). Subgroup analyses of VE were performed for the primary endpoints and secondary endpoint of severe COVID-19 cases. Additional post hoc analyses of subgroups defined by comorbidity risk assessment were performed. Secondary efficacy was analysed in the same manner as primary efficacy (Section 2.5.4.1.2.2), using the cases definitions for severe COVID-19 and CDC criteria for COVID-19

Statistical methods

The estimands to evaluate the efficacy objectives were based on evaluable populations for efficacy. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE was also analysed by all-available efficacy population.

The evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1),and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. This was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy populations, including all randomized participants who completed 1 and 2 vaccination doses respectively, were also performed.

The two primary endpoints were tested hierarchically. Key secondary efficacy endpoints were evaluated sequentially in a prespecified order after the primary endpoints were met. Missing data were not imputed for the primary or secondary analyses. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with MNAR assumption.

VE was estimated as follows: 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose.

A Bayesian approach was used for the primary and secondary endpoints. A beta prior, beta (0.700102, 1), was used for θ = (1-VE)/(2-VE). The prior was centred at θ = 0.4118 (VE=30%). The 95% interval for θ is (0.005, 0.964) and the corresponding prior 95% interval for VE is (-26.2, 0.995). The Bayesian approach was not used for the point estimate for VE. At final analysis, efficacy was to be declared if the posterior probability of VE greater than or equal to 30% ("p") > 98.60%.

During Phase 2/3, 4 interim analyses (IAs) were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. The final analysis was to be performed when 164 cases were observed. However, only one interim analysis was performed, at 94 cases. The final analysis was performed with 170 cases. At the time of the IAs, futility and VE with respect to the first primary endpoint were planned to be assessed. The IA that was performed was successful, as was the final analysis, and results were consistent with the IA.

The success threshold for each interim analysis was to be calibrated to protect overall type I error at 2.5%. The risk of falsely concluding the VE to be above 30% (the type I error rate) with the proposed Bayesian model and over the interim analyses and final analysis under assumption of 30% vaccine efficacy is 0.021 (one sided). Hence the type I error rate for the primary endpoint is controlled. Although only one interim analysis was performed, the overall Type I error (overall probability of success when true VE=30%) was controlled at 0.025 with the originally proposed success/futility boundaries.

Although Bayesian analysis are not usually accepted as confirmatory evidence in pivotal trials, the magnitude of the effect in this study, makes this concern redundant. Hence, the conclusions of the inference are considered robust.

Results

Disposition of All Randomised Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	Placebo (N[a]=18892) n[b] (%)	Total (N[a]=37796) n[b] (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post–Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)

Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	4 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	48 (0.3)	81 (0.4)	129 (0.3)
Withdrawal by subject	45 (0.2)	9 (0.0)	54 (0.1)
Adverse event	20 (0.1)	12 (0.1)	32 (0.1)
Pregnancy	4 (0.0)	4 (0.0)	8 (0.0)
Physician decision	2 (0.0)	1 (0.0)	3 (0.0)
Lost to follow-up	0	2 (0.0)	2 (0.0)
Medication error without associated adverse event	0	1 (0.0)	1 (0.0)
Other	2 (0.0)	1 (0.0)	3 (0.0)
Withdrawn from the study	180 (1.0)	259 (1.4)	439 (1.2)
Withdrawn after Dose 1 and before Dose 2	132 (0.7)	164 (0.9)	296 (0.8)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	44 (0.2)	84 (0.4)	128 (0.3)
Withdrawn after 1-month post–Dose 2 visit	4 (0.0)	11 (0.1)	15 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to follow-up	80 (0.4)	86 (0.5)	166 (0.4)
Adverse event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	3 (0.0)	5 (0.0)
Physician decision	1 (0.0)	2 (0.0)	3 (0.0)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	3 (0.0)	6 (0.0)

Note : 1 subject was randomised but did not sign informed consent and is not included in any analysis population
Note: because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30µg) and one dose of placebo
Note: HIV-positive subjects are included in this summary but not included in the analysis of the overall study objectives.
a. N=number of randomised subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations
b. n=number of subjects with the specific characteristics

Recruitment

This study is ongoing, and participants are continuing to be enrolled and evaluated in Phase 3.

Subject First Visit: 29 April 2020

Data Cut-off dates:

- 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
- 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
- 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)

As a result, 44,822 subjects have been enrolled and 43,386 subjects have been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

Conduct of the study

This study has gone through extensive changes or amendments. The amendments of the phase 1 of the study are deemed acceptable for a dose-finding design. Protocol amendments concerning the phase 3 of the study are overall adequately motivated and acceptable, since they are not expected to affect the conclusions on efficacy. Main Amendments have allowed to include adolescents from 12 to 15 years in the study and added corresponding objectives. Furthermore, secondary efficacy endpoints to include COVID-19 cases that occurred from 14 days after the second dose were added. The SAP was amended twice in line with protocol amendments.

Baseline data

Overall, demographic characteristics were well balanced between study groups.

Demographics (population for the primary efficacy endpoint)[a]

	Comirnaty (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
75 through 85 years	799 (4.4)	807 (4.4)
>85 years	5 (0.0)	5 (0.0)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.

c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥ 30 kg/m^2)
   - Diabetes (Type 1, Type 2 or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Baseline comorbidities - safety population 38,000 subjects- at final analysis:

Table 3. Baseline Charlson Comorbidities ~ 3800 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Charlson Comorbidity Index Category	**BNT162b2 (30 µg) (N[a]=18860) n[b] (%)**	**Placebo (N[a]=18846) n[b] (%)**	**Total (N[a]=37706) n[b] (%)**
Subjects with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any Malignancy	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascular Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congestive Heart Failure	88 (0.5)	83 (0.4)	171 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	99 (0.5)	113 (0.6)	212 (0.6)
Diabetes Without Chronic Complication	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hemiplegia or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Leukemia	12 (0.1)	10 (0.1)	22 (0.1)
Lymphoma	22 (0.1)	32 (0.2)	54 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulcer Disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal Disease	123 (0.7)	133 (0.7)	256 (0.7)
Rheumatic Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:21) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_p3_saf

The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease

not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Numbers analysed

The disposition of the efficacy populations is described in the Table below. There was an imbalance between the two study groups on the number of subjects excluded from the evaluable efficacy population. The two reasons responsible for this imbalance were "Dosing/administration error, subject did not receive correct dose of vaccine" (n=105 in vaccines and n=3 in placebo) and "IP administered that was deemed not suitable for use by Almac" (n=144 in vaccines and n=0 in placebo). There may be several explanations for this imbalance as listed below:

- As the placebo was a fixed volume of saline, with no dilution required, the likelihood of a dosing error in the placebo group was lower compared to vaccine, which did required dilution.
- An isolated dosing/administrative error event in one clinical centre affecting a higher number of participants receiving BNT162b2 (n=52 participants) has contributed to this imbalance.
- Almac was responsible for determining suitability for use of investigational product that was subject to a temperature excursion. Due to the differences in the required storage conditions (ambient for the placebo versus ultracold for the BNT162b2), temperature excursions were not an issue for the placebo but were for BNT162b2.

The protocol design was such that, if a participant experienced any of the specified trigger symptoms that could indicate COVID-19, a potential COVID-19 illness visit should occur, including obtaining a swab for the central laboratory.

Table 4 Efficacy Populations

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			

Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

Outcomes and estimation

Primary Efficacy Endpoints – Final Analysis

The result for the first primary efficacy analysis is shown in Table 5. VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group.

Table 5 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2 (Table 6). VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with and 9 and 172 cases in the BNT162b2 and placebo group, respectively.

Table 6 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

However the seropositive subjects were not many: among 38,000 subjects there were 407 individuals seropositive in the vaccine group and 436 in the placebo group in the age strata 16-55 YOA, and 150 individual seropositive in the vaccine group and 152 in the placebo group in the >55 YOA age strata.

All Confirmed Cases of COVID-19 After Dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on onset of protection.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 7, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group (Table 7). Notably, in the BNT162b2 group, most cases occurred before Dose 2.

Figure 9 displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group. From table 7 and figure 9 it is evident that the first dose offers partial protection, while few cases occur after the second dose.

Table 7 Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

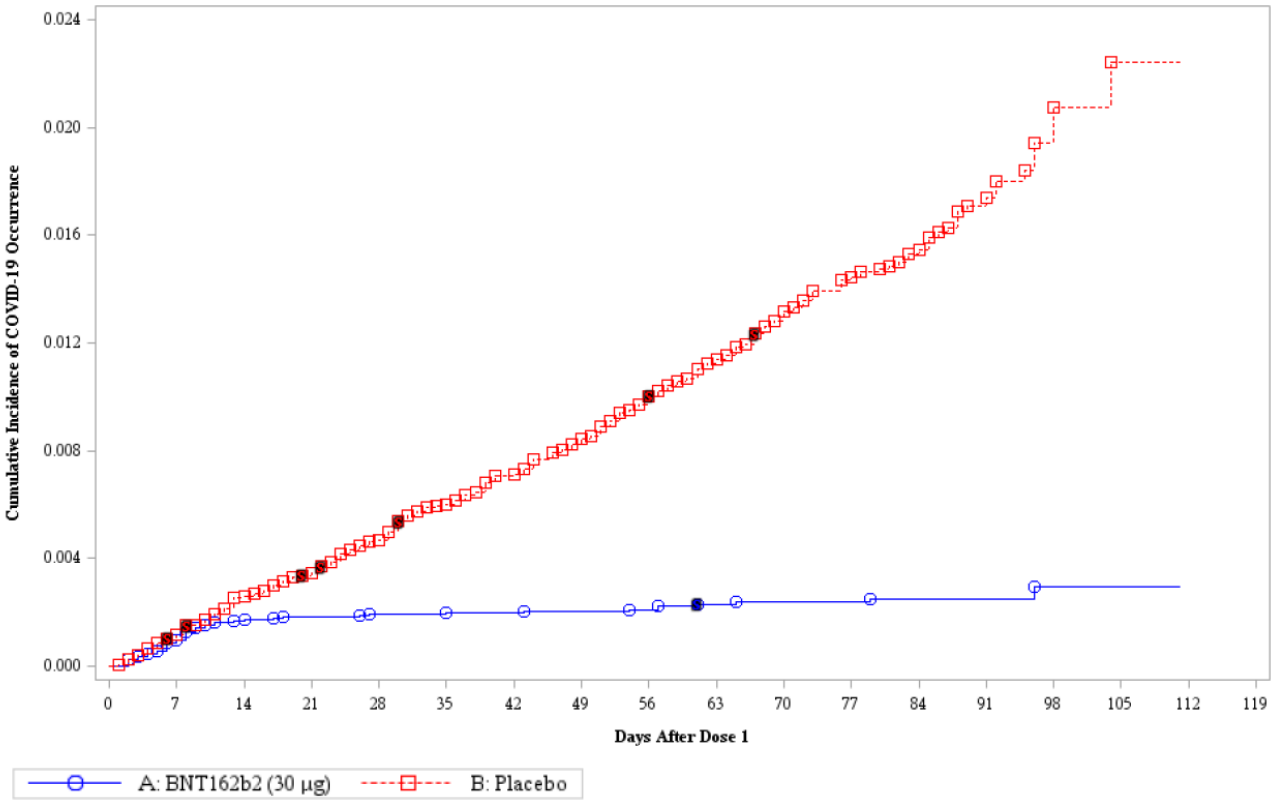


Figure 9. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Immunogenicity results

The immunogenicity part of study C4591001 are presented in this section and aimed to confirm the conclusions on safety and immunogenicity from phase 1. These are the only immunogenicity results from a larger study population available at this stage, and further results from phase 3 are expected post approval. In addition, any data generated in attempts to establish a serological correlate of protection are expected to be reported when available.

The results of the immunogenicity analyses here reported are generated from the Dose 2 evaluable immunogenicity population; baseline positive participants (by N-binding antibody or positive NAAT at Visit 1) were not excluded from these analyses.

SARS-CoV-2 Neutralizing Titres and S1-Binding IgG Concentrations GMTs/GMCs

At 1 month after Dose 2 (Day 52) of BNT162b2, there were substantial increases in SARS-CoV-2 50% neutralizing GMTs (Figure 10) and S1-binding IgG concentrations (GMCs) (Figure 11). GMTs/GMCs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Similar trends were observed for the SARS-CoV-2 90% neutralizing GMTs (data not shown in this report).

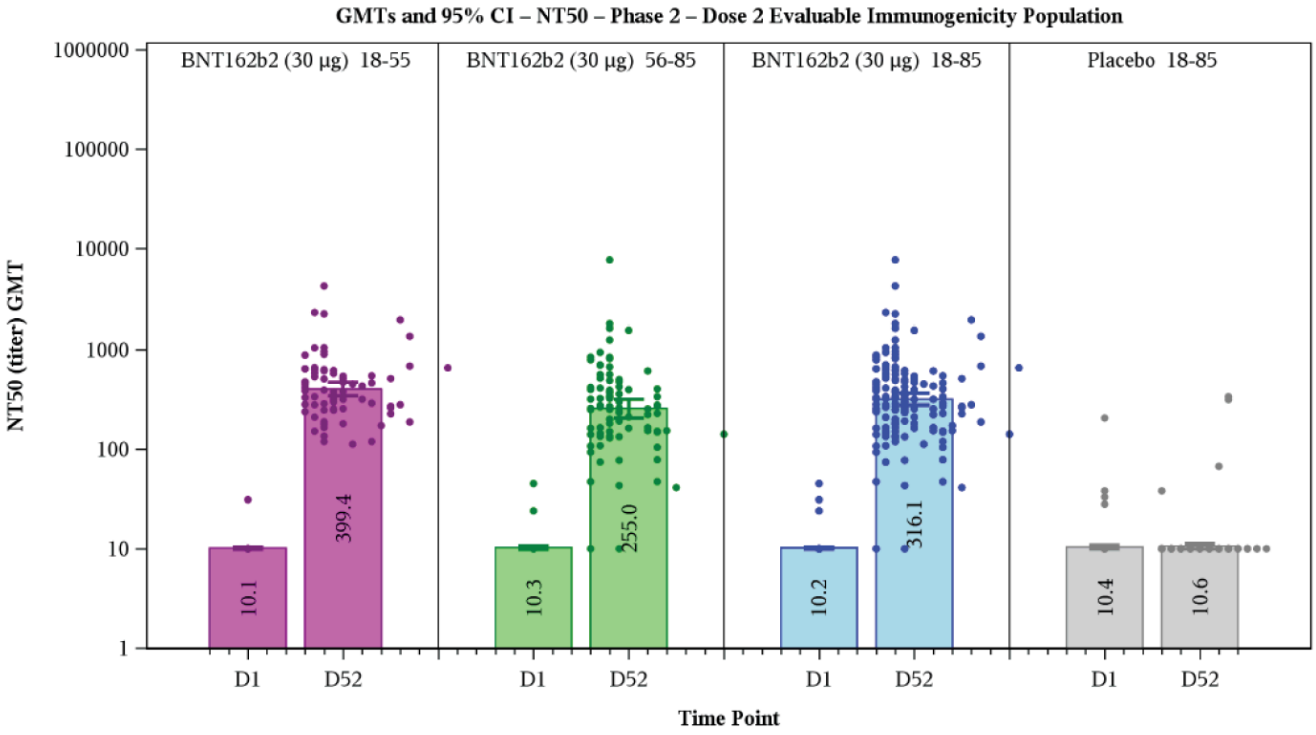


Figure 10. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – NT50 – Phase 2 – Dose 2 Evaluable Immunogenicity Population

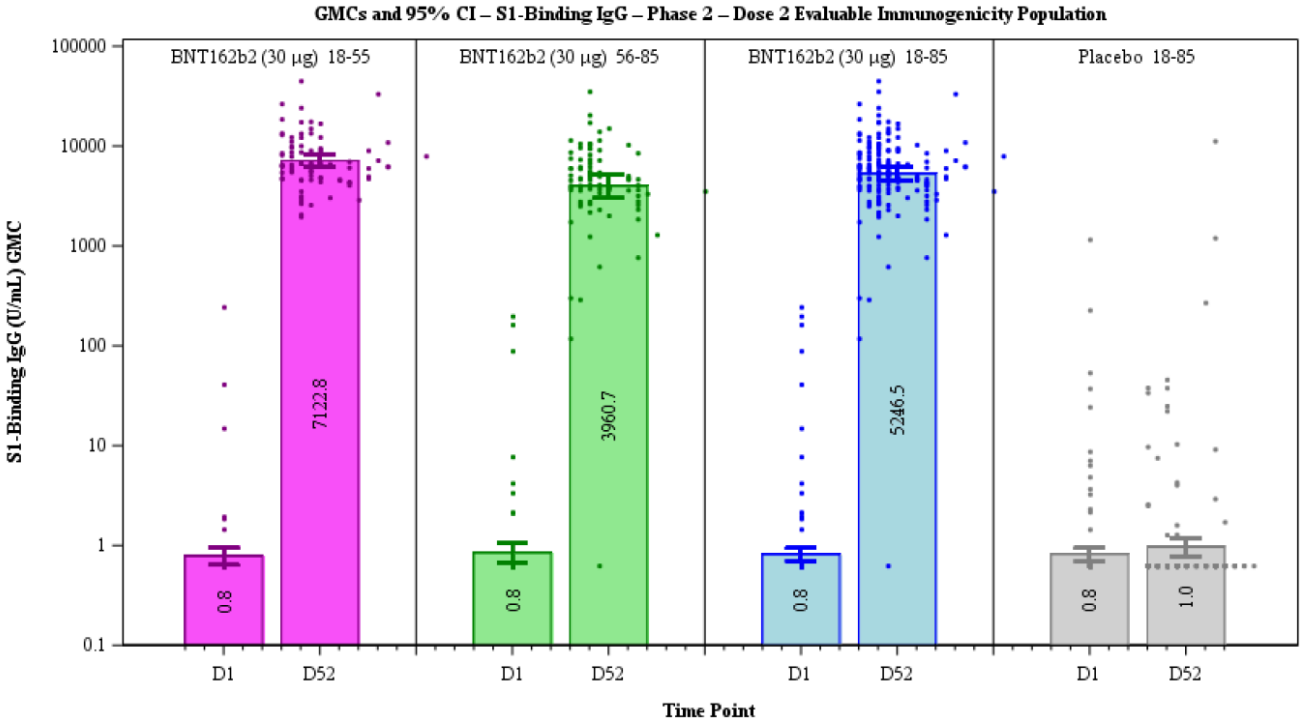


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay – Phase 2 Dose 2 Evaluable Immunogenicity Population

A few participants in the Dose 2 evaluable immunogenicity population had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants. In general, at 1 month after Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status (n=3) were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163).

Ancillary analyses

Vaccine Efficacy by Subgroup

For both primary endpoints, VE was also evaluated for subgroups of participants by age, sex race/ethnicity, and country, without evidence of prior infection (Table 8). Results for additional age groups are shown in Table 9.

Post hoc analyses of efficacy by risk status were performed. For these analyses, at-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥30 kg/m2) (table 11). Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

These subgroup analyses are considered of importance. There is no evidence of significantly reduced efficacy in older age groups, i.e. >90% vaccine efficacy even in over 75-year-old subjects, although not statistically significant as there were only few cases in this age stratum. There were no cases in the 16-17-year-old age stratum, but efficacy is not anticipated to be lower in younger age groups compared to the overall study population. Additionally, it is reassuring that other factors, e.g. ethnicity/race, gender did not impact efficacy. Efficacy was not demonstrated in subjects who were

seropositive at baseline, but the subgroup was very small and results are considered inconclusive rather than negative at this stage.

Table 8 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 9 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; VE= vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.

i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

Table 10 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

Vaccine efficacy by different age subgroup is shown below in line with the information included in the SmPC.

Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection and participants with or without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine N[a]=18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=18,325 Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Vaccine efficacy for Severe COVID-19 cases, Final analysis

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 12). The posterior probability for the true vaccine efficacy greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Consequently, statistical testing of subsequent secondary endpoints (i.e., the additional secondary endpoints related to severe disease with pre-specified control of overall type 1 error) ended. However, descriptive summaries for the additional endpoints were provided.

Table 12 Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial C4591001

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer- Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals		
Study identifier	C4591001	
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled	
	Follow-up for efficacy	Until nov 14, 2020
	Follow-up for safety	At least 1 month, median 2 months
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy	
Treatments groups	Active arm	BNT162b2 (30 µg), 2 doses, 21 days apart, randomized 22 000

	Control arm		Saline placebo, 2 doses, 21 days apart, randomized 22 000
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2
	Second Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.
	Secondary Endpoint	VE-14d-no-no/yes-SARS-Cov-2	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
	Secondary Endpoint	VE-7d/14d-no-no/yes-SARS-Cov-2-Severe	Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
Database lock	November 14, 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Per protocol, Evaluable Efficacy population		
Effect estimate per comparison VE=100x (1- IRR) IRR= caseN/groupN Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time., Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.	Primary endpoint	VE-7d-no-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=8/18198 Cases in Placebo arm N= 162/18325
		Vaccine Efficacy VE %	95.0
		95% Credible Interval	90.3, 97.6
		Pr (VE >30% |data)	>0.9999
	Co-Primary	VE-7d-no/yes-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=9/18559 Cases in Placebo arm N= 169/18708
		Vaccine Efficacy VE %	94.6
		95% Credible Interval	89.9, 97.3

		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no- SARS-CoV-2	Cases in Active arm N=8/18175 Cases in Placebo arm N= 139/18261
		Vaccine Efficacy VE %	94.2
		95% Credible Interval	88.7, 97.2
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no/yes-SARS-CoV-2	Cases in Active arm N=8/19965 Cases in Placebo arm N= 144/20171
		Vaccine Efficacy VE %	94.4
		95% Credible Interval	89.1, 97.3
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-7d-no-SARS-CoV-2-Severe	Cases in Active arm N=1/18198 Cases in Placebo arm N= 3/18325
		Vaccine Efficacy VE %	66.4
		95% Credible Interval	-124.8, 96.3
		Pr (VE >30% |data)	0.7429
Notes	Subgroup analyses support the overall results, e.g. elderly and patients with risk factors appear to be protected as well.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the selected vaccine BNT162b2 was investigated in one pivotal trial, BNT162-02 study. This is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. Safety and immunogenicity data generated during the phase 1 portion of this study supported the selection of BNT162b2 at 30 µg, as a prime/boost regimen (separated by 21 days) as the vaccine candidate to proceed into Phase 2/3.

Phase 2/3 was designed to evaluate the efficacy of BNT162b2, and to provide additional safety and immunogenicity data in a larger population. The study design for the pivotal phase 3 study is overall acceptable and in line with applicable guidelines. In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for

up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. It is an observer-blind study, which is considered acceptable as placebo and vaccine differed in appearance. Randomisation and blinding were considered acceptable.

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (46%, e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Immunocompromised subjects and pregnant or breastfeeding women were excluded from the study. Subjects with known stable infection with HIV, HBV, HCV could be enrolled. Further, individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the immunogenicity of the vaccine.

The study mainly recruited in the USA, but other sites worldwide were also included.

The primary endpoint (laboratory confirmed symptomatic COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 7 days after receipt of the second dose, and then in all participants regardless of serostatus) is considered relevant for the purpose of establishing vaccine efficacy.

SARS-CoV-2 genomic RNA has been detected in nasal swab samples using Cepheid Xpert Xpress SARS-CoV-2 PCR assay on the GeneXpert Molecular Diagnostic System. This method detects 2 structural genes of SARS-CoV-2: E and N2. A validation of this method was performed, and in addition the test was issued a EUA by FDA. In order to assess the analytical detection limit, live virus and commercial control (AccuPlexTM SARS-CoV-2) were used. Clinical sensitivity and specificity were evaluated in comparison with results obtained using another FDA authorised real-time RT-PCR method with positive or negative clinical specimens and pre-pandemic samples. Results showed that Cepheid Xpert Xpress PCR assay is a sensitive and specific method for the detection of SARS-CoV-2 RNA in nasal swabs. The positive rate of self-swab is similar to site-swab, 3.7% and 4.7% positive from self-swab and site-swab respectively in the BNT162b2 group.

The third main secondary endpoint evaluated vaccine efficacy against severe cases of the disease (defined as confirmed COVID-19 with the presence of at least one of pre-defined severity criteria), to determine whether the vaccine decreased the incidence of confirmed severe COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection, 7 to 14 days after the second dose. Prevention of severe disease is an important endpoint, but the relative rarity of severe cases would require either a very large study population and/or a very long study duration to be certain to achieve sufficient statistical power. Therefore, it is acceptable as a secondary endpoint.

The immunogenicity secondary and exploratory endpoints are considered acceptable.

This is an event-driven study. This case-driven approach is deemed appropriate as the rate of accumulation of cases was not certain which could allow a rapid assessment of efficacy in case of a high attack rate. With assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. The randomisation procedure is considered appropriate to control confounding factors.

The statistical methods are overall acceptable. The Bayesian approach used is not expected to affect the decisions from the hypothesis testing procedure. For consistency and ease of interpretation, the Clopper Pearson confidence intervals will be included in the SmPC rather than the Bayesian credible intervals. Of the four pre-planned interim analyses only one was performed, and the final analysis was also submitted. These analyses give highly consistent results with VE far from the null hypothesis limit

of 30%. Confidence intervals were not adjusted for multiplicity, which is considered acceptable in this context.

While it could be argued that alpha could be allocated according to a group sequential design, since no failed interim analysis has been performed, the alpha allocated to the interim analysis may be recycled to the final analysis. Hence the final analysis could have been performed at full alpha level and the coverage probability of the "naïve" confidence interval is therefor considered correct.

The interim and final analyses are conducted in an evaluable efficacy population of participants who receive the two doses within the predefined window and excluding subjects with other major protocol deviation, in order to obtain a best-case estimate of vaccine efficacy. However, this approach could result in bias due to exclusion of subjects. For this reason, sensitivity analyses assessing VE based on all laboratory-confirmed cases with symptom onset at any time after the first dose (dose 1 all-available efficacy population) and 7 days after the second dose (dose 2 all-available efficacy population) have been performed without excluding participants with major protocol deviations.

Overall, the study report including the final analysis is considered adequate. This is not the final report for the study, as the study is expected to continue for a total of 24 months.

Baseline data

At the cut-off date of 14 November 2020, the disposition of the 38,000 participants were similar in the BNT162b2 and placebo groups. Overall, 0.2% of participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%). The reasons for discontinuation were also balanced. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reason was previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AEs (0.1% in both treatment groups).

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. Overall, most participants were White (82.8%) and non-Hispanic/non-Latino (72.7%) (26.8% of Hispanic/latino ethnicity), median age was 52.0 years, and approximately 49% were female. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). In 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy).

Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. Obese participants made up 35.1% of the safety population. Overall, 120 subjects were HIV-positive and were evenly distributed between treatment groups.

Efficacy data and additional analyses

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

The first interim analysis for vaccine efficacy (VE) was conducted on 08-Nov-2020 by an IDMC. The data cut-off date was 04-Nov-2020, when a total of 94 confirmed COVID-19 cases were accrued. There were 4 COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the

placebo group. These data gave a vaccine efficacy of 95.5% (95%CI: 88.8%, 97.5%) among participants without evidence of infection up to 7 days after Dose 2, and a >99.99% posterior probability for the true vaccine efficacy greater than 30% conditioning on available data. Participants included in the first interim analysis were also included in the final analysis.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was high, 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after dose 2 was 94.2%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively) with a posterior probability (VE≥30%/data) of >99.99%.

Slightly more subjects in the placebo group had symptoms of COVID-19 without being a confirmed case by PCR. This is also reflected in slightly more subjects in the placebo arm with result not available from the swab. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with the available data, assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavourable for efficacy results of the study. 500 imputations were performed that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level. VE after imputation was over 80% also with up to 15-fold increase of positivity rate applied to the BNT162b2 group. Hence, there is no concern that this slight imbalance has introduced any significant bias to the results presented below.

The 2-dose schedule is considered justified both based on immune responses and on the actual efficacy results. In dose 1 all-available efficacy (mITT) population, regardless of evidence of infection before or during the vaccination regimen, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group (n=21,314 subjects) compared to 275 cases in the placebo group (n=21,258 subjects). Notably, in the BNT162b2 group, most cases (36/(50)) occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after dose 1 but before dose 2.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverge with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months post-dose 2, the BNT162b2 cumulative curve is stable which would not suggest waning protection. A longer follow-up is necessary to investigate the duration of the efficacy of the vaccine in protecting against the disease.

For both primary endpoints, no clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%. Efficacy was consistent across relevant subgroups.

The results in elderly are of great importance, as increasing age is an identified risk factor for severe disease and death. The results from this study are therefore reassuring suggesting a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9). There was no indication of

decreasing efficacy in subjects ≥75 years although the number of cases was small (0 in the vaccine group and 5 in placebo). In addition, the number of subjects >85YOA is very limited (5 subjects) hence the impact of immunosenescence on vaccine efficacy in these very old individuals remain uncertain.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for participants at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, obese with body mass index (BMI) ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, hypertension) was 95.3%, as compared with 94.7% for those not at risk. VE for participants ≥65 years of age and at risk was 91.7%, as compared with 100% for those ≥65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. The VE by comorbidity status are as follows: cardiovascular (VE 100.0 (-0.8, 100.0)), Chronic pulmonary disease (93.0 (54.1, 99.8)), diabetes (94.7 (66.8, 99.9)), Hypertension (95.4 (82.6, 99.5)).

Severe disease cases were uncommon in the study: 1 case in the vaccine group and 4 cases in the placebo group (one case in the all evaluable population) after 7 days post second vaccination. None of the severe cases were baseline positive for SARS-CoV-2.

In the evaluable efficacy population, subjects without evidence of prior SARS-CoV-2 infection, the estimated VE against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%: 96.3%). The posterior probability for the true VE greater than 30% is 74.29% (7 days) and 74.32% (14 days), which did not meet the pre-specified success criterion for this endpoint, therefore no reliable conclusion can be drawn at this stage. While data on severe COVID-19 are limited, the experience with other vaccines (rotavirus and influenza vaccines with known efficacy against mild disease but better efficacy against severe disease) coupled with the high observed vaccine efficacy observed for BNT162b2 on all COVID-19 cases in populations with any comorbidity gives reassurance that the vaccine is likely to prevent severe disease. However, a precise estimate of its protective effect is presently lacking. The final study report may include additional data to the extent that the study is continued in a randomised fashion with a placebo group.

The second primary endpoint -VE in participants with and without prior evidence of SARS-CoV-2 infection- yielded similar results as the one in the population excluding those without evidence of prior infection. However, analysis is largely driven by events in subjects without evidence of prior infection, and therefore does not provide additional information.

It is not possible to conclude on vaccine efficacy in subjects with prior COVID-19, or signs of infection with SARS-CoV2 because only a small number of subjects were found to be seropositive at baseline (approximately 550 in each vaccine and placebo group), and only 2 cases of disease were reported in this subset (1 in each group). Further data may become available as the trial proceeds, but it is unlikely that the study will be able to deliver conclusive evidence for a number of reasons (e.g. it is very likely that the number of subjects seropositive will remain limited, and that there will be a lower incidence of disease in seropositive placebo recipients compared to seronegative placebo recipients due to existing partial protection). The extent of additional protection in seropositive subjects is presently uncertain. Effectiveness studies may give us some information on this regard.

Genome sequencing of the SARS-CoV-2 strains in the BNT162b2 vaccine and placebo groups has not been performed. However, this work is planned by the Applicant.

The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This correspond to about 1.5 months of median follow-up time duration after completion of the full vaccination regimen. Therefore, available efficacy data are limited in term of follow-up duration, and the efficacy of the vaccine over longer-time remains unknown. Data are expected to become available post-authorisation.

Immune responses in terms of neutralising antibodies were measured in the phase 1 and 2 part of the study. Overall, the immune responses measured in the phase 1 and 2 part of the pivotal study are consistent and in line with the phase 1 study BNT162-01 results. As expected, both neutralising antibody levels and S-protein binding antibody levels were higher in the youngest age stratum compared to the older age stratum. Serum titres in vaccinated subjects were numerically higher compared to human convalescent sera, up to 1 month after dose 2. There is presently no established correlate of protection.

Very limited results by baseline serostatus were provided, but updated immunogenicity data is expected to become available.

Cell mediated immune responses were demonstrated in the phase 1 part of the study as well as in the other phase 1/2 study BNT162-01, but in a small cohort of subjects only. A clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED.

In total 14 adolescents aged 12-15 years were included in the vaccine group and 13 in the placebo group, and 52 adolescents aged 16-17 years in the vaccine and 55 in the placebo group. Vaccine efficacy could not be estimated for these subjects as no cases of disease were reported. No immune response data are available. However extrapolation of efficacy is possible from young adults because, from an immune system perspective, adolescents do not differ from young adults, thus there are no reasons to believe that the vaccine will not be as efficacious at least in the age subgroup proposed for the current indication (>16 years).

At cut-off date (14-Nov-2020), 120 subjects HIV positive were vaccinated with BNT162b2. Immunogenicity and efficacy data are not available at this time but will be provided post-authorisation.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Excellent vaccine efficacy (preventing symptomatic COVID-19) was shown in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%), which was consistent across relevant subgroups. It is likely that the vaccine also protects against severe COVID-19, though these events were rare in the study, and statistically certain conclusion cannot be drawn. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

The candidate vaccine BNT162b2 at 30 µg given twice 21 days apart was assessed a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and a Phase 1/2/3 study (C4591001) was initiated shortly afterwards in the United States (US). Hence, the safety data base for BNT162b2 constitutes of two Phase 1 studies (BNT162-01 and C4591001) and one Phase 2/3 study still ongoing (C4591001).

The cut-off for safety data included in this assessment is 14 November 2020.

The two Phase 1 trials (BNT162-01 and C4591001) are described in previous sections. Study C4591001 was initially started as a Phase 1/2 study in the USA and was then amended to expand to a global Phase 3 study.

Phase 2/3 of Study C4591001 included subjects that were stratified into two age groups: 18-55 years and >55-85 years. The Phase 3 part however was subsequently amended (6 Sept 2020 protocol amendment) to include subjects from 16 years of age in the younger age group (and then from 12 years of age) and subjects >85 years of age in the older age group.

AEs were collected during the Phase 2/3 study from the signing of the informed consensus document through and including 1 month after Dose 2 (visit no. 3). In addition, in all follow-up visits where blood samples for immunogenicity data are taken, any AEs and SAEs as appropriate occurring up to 48 hours were recorded after each visit. Immunogenicity follow-up is planned to occur during that period with visits 1-month, 6-months, 12-months and 24-months post the first vaccination. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. SAEs are recorded for up to 6 months after Dose 2 (ongoing at the time of this submission). In addition, any potential COVID-19 illness will lead to extra visits followed by convalescent visits. At the cut-off date 14-Nov-20, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall the study enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up.

The assessment is based on the following safety data (cut-off date 14 Nov 2020):

- Phase 1: i) Study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=18); ii) Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=0).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536). This subset constitutes the core safety data set in this assessment.
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up. In this population, the total number of subjects 16-17 years were 283 (N=138 BNT162b; N=145 placebo) and 100 participants were 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group).
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Among these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).
- Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events,

and antipyretic/pain medication usage for 7 days after each dose by using an e-diary. Eight subjects aged 16-17 years were included in this subset (BNT162b2 N=5; placebo N=3).

2.6.1. Patient exposure

Distribution and Exposure were presented for the population with median follow up of 2 months and for the whole population. Of the 37,796 subjects in the group with median follow up of 2 months who were randomized in the study before 9 October 2020, 90 participants (0.2%) were excluded from the safety population (89 did not receive study intervention and 1 did not provide informed consent).

		BNT162b2 N = 18904	**Placebo N = 18892**
		N (%)	**N (%)**
Median follow up 2 months (at least one month after dose 2)	Randomized	18904 (100%)	18892 (100%)
	Vaccinated with Dose 1	18858 (99.8%)	18849 (99.8%)
	Vaccinated with Dose 2	18553 (98.1)	18534 (98.1%)
HIV positive		59	61
Follow up ≥ 2months after dose 2		9531 (50.5%)	9536 (50.6%)
Follow up ≥ 10 to < 12 weeks after dose 2		2853 (15.1%)	2809 (14.9%)
Follow up ≥ 12 to < 14 weeks after dose 2		382 (2.0%)	398 (2.1%)

For Dose 1, three participants randomized to the placebo group received BNT162b2, and two participants randomized to the BNT162b2 group received placebo. For Dose 2, four participants randomized to the placebo group received BNT162b2, and five participants randomized to the BNT162b2 group received placebo.

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the BNT162b2 (93.1%) and placebo (92.9%) groups.

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cut-off.

In total 1145 individuals of the safety population were SARS-CoV-2 seropositive at baseline.

A high exposure rate of 99.8% to the first dose was reached in both vaccine and control arm and a small number of individuals were withdrawn after the first dose, leading to a high rate of exposure to the second dose in both study arms (98.2% and 98.1%). Reasons for withdrawals (1.0% and 1.4%, respectively) were in most cases withdrawals by the participant, or loss to follow-up.

There were no clinically meaningful differences in the safety population by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Table 14 Safety Population, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis

Baseline SARS-CoV-2 Status		Vaccine Group (as Administered) BNT162b2 (30 µg) n[a]	Placebo n[a]	Total n[a] (%)
Positive	Randomized[b]			1148
	Vaccinated	557	588	1145 (99.7)
	Safety population	557	588	1145 (99.7)
	HIV-positive	12	8	20 (1.7)
	Excluded from safety population			3 (0.3)
	Reason for exclusion			
	Subject did not receive study vaccine			3 (0.3)
Negative	Randomized[b]			35764
	Vaccinated	17885	17858	35743 (99.9)
	Safety population	17884	17858	35742 (99.9)
	HIV-positive	43	50	93 (0.3)
	Excluded from safety population			22 (0.1)
	Reason for exclusion			
	Subject did not receive study vaccine			21 (0.1)
	Did not provide informed consent			1 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (07:27)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adsl s003 saf pop bs p3

The disposition, exposure and withdrawal profile of the whole study population was comparable to the group that was randomised before 9 October 2020 with median follow up of 2 months.

Among the 37,706 subjects with a median follow-up of 2 months, 50.6% had ≥2 months duration of follow-up after Dose 2 and 91.6% had a duration of follow-up time of ≥1 month after Dose 2. Around 3000 individuals have already a follow of at least 10 weeks after dose 2. Updates, including additional safety data as well as assessment of the differences in safety profile in the longer follow-up compared to the initial safety dataset, if any, shall be provided when more mature data will be available.

Six-months post Dose 2 follow-up data from the first ~6000 subjects are expected by the end of February 2021 and this will allow a relevant discussion on the safety profile versus the initial dataset.

Based on the population with a median follow up of 2 months, demographic characteristics are considered well balanced between vaccine and placebo arm. Most included subjects were white (83%), with a median age of 52 years. A balanced distribution is seen regarding gender (51% male, 49%

female). The younger and older age groups were 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Of note, 35% of individuals were obese in both study arms. Across both treatment groups, 20.7% had any comorbidity.

The number of subjects with any Charlson co-morbidity diagnoses was balanced in both study arms (20%). Most prevalent were the diagnoses diabetes mellitus (7.8%) and COPD (7.8%) followed by subjects showing any type of malignant disease (3.9% in vaccine and 3.5% in placebo group). Other diagnoses were abundant with ≤ 1% in both study arms (population with a median follow up of 2 months). In the population with a follow-up ≥2 months, Charlson co-morbidity diagnoses was similar.

The demographic distribution was somewhat different when comparing seropositive and seronegative individuals, observing a median age of 43 years in seropositive and of 52 years in seronegative individuals. Furthermore, the seropositive group covered a higher proportion of obese individuals (42.2% versus 34.7%). Demographic characteristics in the whole population were comparable to those seen in the population with a median follow up time of 2 months.

2.6.2. Reactogenicity

Reactogenicity was evaluated in a subset of the Phase 2/3 study of 8,183 subjects (BNT162b2 n=4093; placebo n=4090) from both age groups (16 to 55 and >55 years of age) that received BNT162b2 or vaccine according to the proposed dosing regimen. Of note, the number of subjects aged 16-17 years included in this subset was limited (n=8; BNT162b2 n=5; placebo n=3). After each dose, the subjects reported any local reactions, systemic events, including antipyretic/pain medication usage for 7 days, by using an e-diary (cut-off date 14 Nov 20).

Local reactions

The most commonly reported local reaction among the subject that received BNT162b2 was pain at the injection site, which occurred slightly more common among subjects 16-55 years (N=2291 [83.1%] post Dose 1; N=2098 [77.8%] post Dose 2) compared to those >55 years of age (N=1802 [71.1%] post Dose 1; N=1660 [66.1%] post Dose 2). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at a lower frequency (16-55 [14.0% and 11.7%]; >55 [9.3% vs 7.7%]).

There was no difference in frequency of redness and swelling at injection site after the two doses of BNT162b2. Redness occurred in about 5-7% in both age groups (16-55 [4.5% after Dose 1, 5.9% after Dose 2]; >55 [4.7% after Dose 1, 7.2% after Dose 2]). Swelling was reported also in about 5-7% of the subjects in both age groups (16-55 [5.8% after Dose 1, 6.3% after Dose 2]; >55 [6.5% after Dose 1, 7.5% after Dose 2]). In the placebo group, redness and swelling were reported infrequently in both age groups (≤1.2%).

Overall, the majority of local reactions were mild or moderate in severity, no Grade 4 reactions were reported. Severe local reactions (≤0.7%) were reported infrequently in the BNT162b2 group after either dose and was more commonly reported in the younger group. Across age groups, local reactions for the BNT162b2 group after either dose had a median onset between 1-3 days (Day 1 was the day of vaccination), with a median duration of 1-2 days.

No clinically meaningful differences in local reactions were observed by baseline SARS-CoV-2 status subgroups. However, since the baseline SARS-CoV-2 positive subgroup included very few participants (vaccinated n=154; placebo n=164), these results should be interpreted with caution.

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population

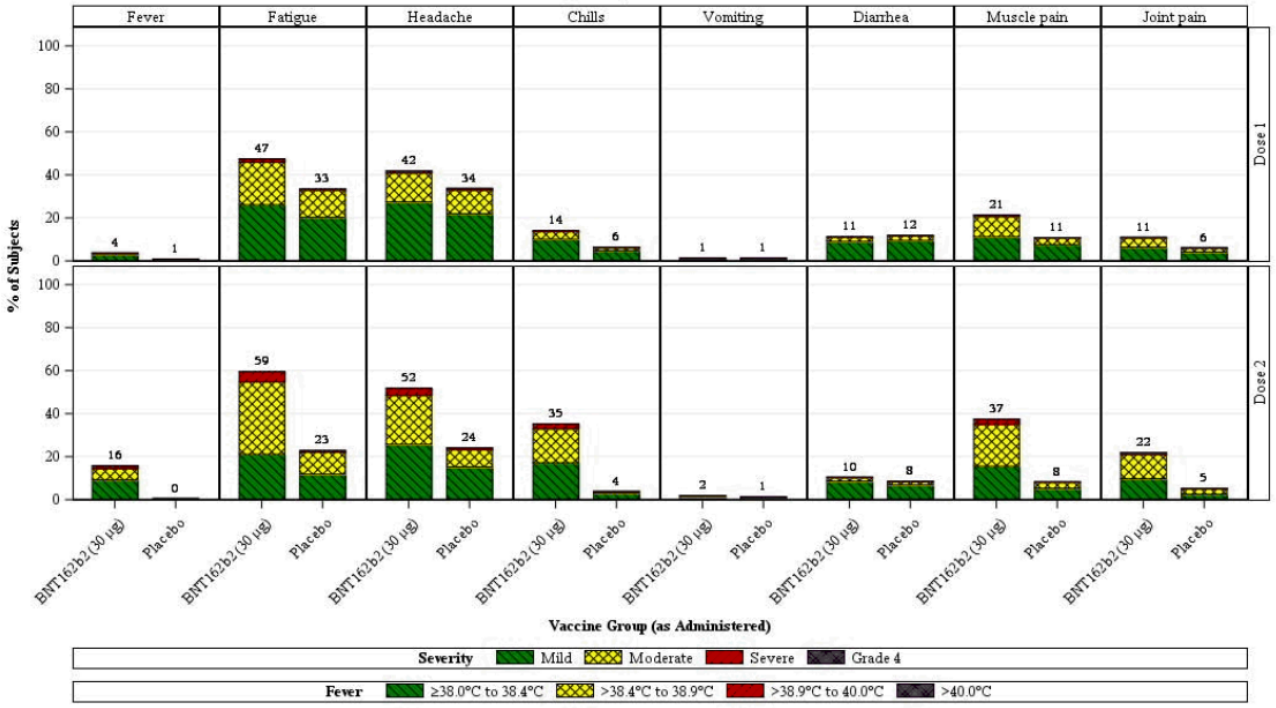
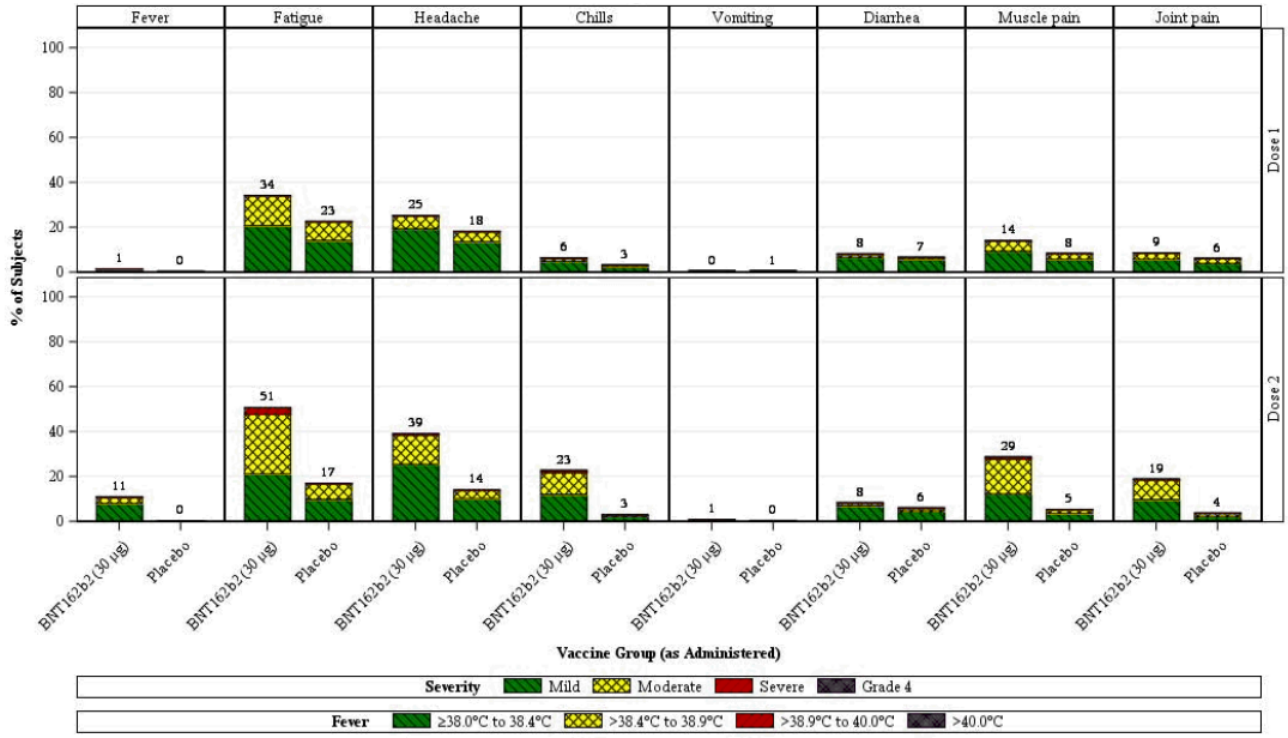


Table 16 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group >55 Years – Reactogenicity Subset for Phase 2/3 Analysis–Safety Population



Systemic events were generally reported more frequently in the BNT162b2 group than in the placebo group, for both age groups and doses. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was 2-3 days, with a median duration of 1 day.

Systemic events were generally increased in frequency and severity in the younger age group compared with the older age group, with frequencies and severity increasing with number of doses (Dose 1 *vs* Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were: fatigue, headache, muscle pain, chills, joint pain and, fever.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%). Of note, medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.8% to 22.0%).

No clinically meaningful differences in systemic reactions were observed by baseline SARS-CoV-2 status subgroups, however as mentioned data in baseline SARS-CoV-2 positive subjects are limited.

Overall, the reported reactogenicity is in line with what can be expected from any vaccine. The local and systemic reactions were transient and of short duration, the majority were mild to moderate at intensity and the reactions were milder among older subjects (>55 years).

2.6.3. Adverse events

In the subset of participants randomised before 9 October 2020 with Median 2 Months of Follow-Up After Dose 2 (N= 37,586; from Dose 1 to 1 month after dose 2) and the subset of participants with at least 2 Months of Follow-Up After Dose 2 (N=19,067; from dose 1 to data cut off 14 November 2020), the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cut-off date for all enrolled participants (N=43,252; from dose 1 to data cut-off 14 November 2020). Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events (see above). This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group (26.7%) compared with the placebo group (12.2%).

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs.

Table 17 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to date cutoff date (14 Nov 2020) – Subjects with 2 months follow-up time after dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Adverse Event	BNT162b2 (30 µg) (N[a]=9531) n[b] (%)	Placebo (N[a]=9536) n[b] (%)	Total (N[a]=19067) n[b] (%)
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related[c]	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related[c]	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:28)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 all 2mpd2 p23 saf

Overall, in participants with 2 months follow up after dose 2, 21.4% / 12.6% (vaccine/placebo) and 13.6%/3.6% experienced at least 1 AE and 1 related AE, respectively. It is noted that the frequency of AEs and related AEs is lower compared to individuals with a median follow up of 2 months (27%/12.5% and 20.8%/5.1%).

The frequency of individuals experiencing AEs were slightly higher in the younger compared to older individuals (29.3% and 23.8% vaccine arm; 13.2% and 11.7% placebo arm). SAEs and deaths were however balanced in both study arms in both age groups.

The frequency of immediate AEs after dose 1 was low in participants with median 2 months of follow-up after Dose 2 (0.4%) and the whole population (≤0.5%), belonging mostly to the SOC general disorders and administration site conditions, primarily injection site reactions. No participant reported an immediate allergic reaction to vaccine.

Severe AEs, SAEs, AEs leading to discontinuation, and deaths were reported by ≤1.1%, 0.6%, 0.0%, and 0.0%, i.e. low and equally distributed in both study arms. No differences vs. the whole population were seen according to age groups.

The rate of AEs and related AEs was slightly higher in the SARS-CoV-2 negative group compared to SARS-CoV-2-positive individuals. Stratification according to serostatus in the safety group median follow up 2 months reveals overall very low numbers of severe AEs, SAEs and deaths.

Table 18 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month after Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subject for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Positive

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=545)	Placebo (N[a]=580)
Adverse Event	n[b] (%)	n[b] (%)
Any event	120 (22.0)	57 (9.8)
Related[c]	90 (16.5)	26 (4.5)
Severe	8 (1.5)	2 (0.3)
Life-threatening	2 (0.4)	0
Any serious adverse event	4 (0.7)	1 (0.2)
Related[c]	0	0
Severe	2 (0.4)	1 (0.2)
Life-threatening	2 (0.4)	0
Any adverse event leading to withdrawal	2 (0.4)	1 (0.2)
Related[c]	0	0
Severe	0	0
Life-threatening	1 (0.2)	0
Death	1 (0.2)	0

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 pd2 bs p3 saf

Table 19 Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Negative

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=17841) n[b] (%)	Placebo (N[a]=17808) n[b] (%)
Any event	4837 (27.1)	2253 (12.7)
Related[c]	3742 (21.0)	911 (5.1)
Severe	205 (1.1)	105 (0.6)
Life-threatening	16 (0.1)	20 (0.1)
Any serious adverse event	97 (0.5)	80 (0.4)
Related[c]	3 (0.0)	0
Severe	54 (0.3)	47 (0.3)
Life-threatening	16 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	31 (0.2)	24 (0.1)
Related[c]	13 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	1 (0.0)	4 (0.0)
Death	0	2 (0.0)

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_pd2_bs_p3_saf

There were 19,067 participants with at least 2 months follow-up time after Dose 2, and similar to the 37,586 participants randomised before 9 October 2020 with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cut-off date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo).

In the younger versus older BNT162b2 age groups, AE SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)

- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

Most often occurring events by PT comprised vaccine typical reactions such as injection site pain, fever, fatigue as well as myalgia and arthralgia. Lymphadenopathy and nausea occurred respectively in 0.4% and 0.6% more cases in the vaccine compared to placebo arm.

Related AEs belonged overall to the same SOCs as described above, i.e. general disorders and administration site conditions (3426 cases, 20.8%), musculoskeletal reactions (1148 cases, 6.1%), and nervous system disorders (979 cases, 5.2%) and occurred overall more often in the vaccine than in the placebo arm (median follow up 2 months). Severe AEs occurred more often in the vaccine arm (1.2% vs. 0.6%) in the subset with a median follow up time of 2 months, reflecting a similar SOC pattern.

The following specific observations are made based on PTs:

Numerical disbalances are observed for several hypersensitivity terms ((drug)hypersensitivity/ immunisation events; 5/3 cases ≥ 2 months group, 13/6 cases whole population, 6/1 cases deemed related in the whole population, 4 cases deemed severe (whole population), in the SOC immune system disorders).

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study, 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and, among those, two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. The participant who received BNT162b2 had a history of allergy to tree pollen. This participant reported Drug hypersensitivity and Urticaria on the day of Dose 1. Both AEs were of moderate severity and lasted one day. The participant did not receive Dose 2 of the vaccine. The participant who received placebo had an allergy to shellfish and iodine. This participant reported Allergy to vaccine and Pharyngeal swelling 1 day after Dose 1. Both events were of moderate severity and lasted 13 days and 10 days, respectively. This participant did not receive Dose 2 of study intervention.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine.

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole population)). However, none of the cases considered related to study drug treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm, which where however balanced in frequency between vaccine and placebo arm.

An imbalance in PT connected to sleep disturbances was noted in the whole population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus the placebo arm).

A slight imbalance of hyperhidrosis/night sweats was noted in the whole population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole population).

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole population).

Stratification according to age did not reveal meaningful differences in the types of AEs.

A stratification according to serostatus was performed in individuals with a follow up of at least one month (median FUP 2 months) and ≥2 months. Most abundant SOCs are similar to the SOCs identified in the general population with ≥2 months follow-up. No additional safety concerns are detected when stratifying according to serostatus.

2.6.4. Serious adverse event/deaths/other significant events

SAEs

This section presents the SAEs reported up to the data cut-off (14-nov-20).

Among the 19,067 subjects (BNT162b2 n=9531; placebo n= 9536) with ≥2 months of follow-up post Dose 2, small percentages of subjects in the 30 µg BNT162b2 group (56 [0.6%]) and the placebo group (53 [0.6%]) reported any SAEs. Subjects in both the BNT162b2 group and placebo group, respectively, reported SAEs at similar rates for the observed SOCs. A similar frequency was observed for the entire study population and no clinically meaningful differences in SAEs were observed by age, baseline SARS-CoV-2 status, ethnicity, race or sex subgroups.

Among all included subjects (BNT162b2 n=21720; placebo n=21728) three SAEs were reported in the SOC immune system disorders. One SAE of anaphylactic reaction (related to bee sting) and one drug hypersensitivity (related to treatment with doxycycline) was reported in the BNT162b2 group. In addition, one SAE of anaphylactic shock (related to an ant bite) was reported in the placebo group.

In the subset of individuals aged 16-17 years old, one SAE (facial bone fracture) was reported.

After the cut-off date and up to 5-Dec-20, additional 22 SAEs have been reported (blinded data).

SAEs related to study intervention

Up to the cut-off date, four of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention. One event of lymphadenopathy and one event of shoulder injury due to incorrected administration were considered related to BNT162b2.

It is not agreed that the event of ventricular arrythmia and the event of pain in the lower back/extremities/and radicular paraesthesia have been convincingly demonstrated to be related to study intervention, since the subjects had underlying conditions that could have caused the two SAEs, there is little biological plausibility, and the overall numbers of reported events do not allow for a causal inference.

Death

Six events of death (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention, which is agreed since other pre-existing diseases were more likely to have caused death than the vaccine. After the cut-off date and up to 5-Dec-20, one additional event of death due to aortic rupture were reported (data blinded).

2.6.5. Laboratory findings

Laboratory results are available for the two Phase 1 studies, but not for the Phase 2/3 trials. This is considered acceptable. Except for minor transient decrease in lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

2.6.6. Safety in special populations

No clinically meaningful differences in AEs were observed by age, country (mostly Argentina, Brazil, USA), ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino), gender and race (With, Black or African American, all other races) subgroups.

Pregnancy

At the time of the data cut-off in the Phase 2/3 study (14 Nov 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes. Thus, data on pregnancy are very limited at this stage.

Elderly

The Phase 2/3 study included >40% of subjects >55 years of age. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). No differences in AE frequency were detected among subjects >70 years of age compared to the older age group >55 year. Thus, no specific safety concern is anticipated for the elderly.

Immunocompromised individuals

Per protocol, participants with chronic stable HIV infection were defined as HIV disease with a documented viral load <50 copies/mL and CD4 count >200 cells/mm3 within 6 months before enrolment, and on stable antiretroviral therapy for at least 6 months. Stratification by CD4 count, efficacy and immunogenicity data are not available at this time but will be provided post-authorisation.

Safety data are available for 196 participants with stable HIV infection. The most frequent AEs in the BNT162b2 group were reported in the General Disorders and Administrative Site Conditions SOC including injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

Assessment of paediatric data on clinical safety

Paediatric individuals age 16 to 17 years of age are included in the Phase 2/3 study that constitutes the safety database in this assessment. The population of subjects aged 16-17 years are limited (n=283). No additional or new AEs were observed compared to adults).

There were no participants in the 16 to 17 years of age group with ≥2 months of safety follow-up at the time of the data cut-off (14 November 2020). The longest duration of follow-up in this age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study.

The reactogenicity subset of ~8000 participants (n=4093 BNT162b2; n=4090 placebo) contributing e-diary data included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) include reactogenicity data (local reactions and systemic events) collected via e-diary up to the safety cut-off date of 14 November 2020. The reported adverse events were primarily reactogenicity events with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

In the reactogenicity subset including individuals aged 12-15 years and the 8 individuals aged 16-17 years, the most frequently reported systemic reaction in both treatment groups were fatigue (59.2% in the BNT162b2 group and 25.5% in the placebo group), followed by headache (57.1% BNT162b2, 43.1% placebo). Fever ≥38°C was reported for 26.5% more participants who received BNT162b2 over placebo; two (4.1%) of these participants reported severe fever (>38.9°C to 40.0°C).

2.6.7. Safety related to drug-drug interactions and other interactions

Interaction studies with other vaccines have not been performed, which is acceptable given the need to use the vaccine in an emergency situation. The Applicant will conduct a study post-authorisation as indicated in the RMP (see section 2.7).

2.6.8. Discontinuation due to adverse events

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn from the study because of AEs. The results were similar to the AEs leading to withdrawal in the group randomised before 9 October 2020 with median follow up of 2 months. Among 19,067 participants with at least 2 months of follow-up time post Dose 2, 1 participant in the BNT162b2 group and no participants in the placebo group had an AE leading to withdrawal from the study.

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal. Among all 43,448 participants, no clinically meaningful differences in AEs leading to withdrawal were observed by age or other subgroups.

2.6.9. Post marketing experience

Post-marketing data are not yet available as the vaccine has not been approved in any country at the time of the data cut-off (14-Nov-20). After the cut-off date, it is noted that several countries have recently authorised the vaccine for emergency use (e.g. UK, Canada, US). Two cases of anaphylactoid reaction out of 138,000 persons vaccinated have been reported in individuals carrying Epipen after initiation of vaccination in one country, which resolved with standard therapy. One case of anaphylaxis was reported in another country (unknown denominator) in a subject without known history of

allergies, which required ICU and was then resolved. Post-marketing safety data are expected with the next monthly summary safety report.

2.6.10. Discussion on clinical safety

The safety database for BNT162b2 constitutes of two Phase 1 studies (BNT162-01[3] and C4591001[4]) and one Phase 2/3 study (C4591001) which is still ongoing. The cut-off date for safety data included in this assessment is 14 November 2020.

Up to the cut-off date ~44,000 subjects had been recruited and received at least one dose of either BNT162b2 (n=21,720) or placebo (n=21,728). The core safety database of this assessment constitutes of ~19,000 participants who have been followed ≥2 months after the 2nd dose of BNT162b2 (n=9531) or placebo (n=9536). The Applicant has also presented data from a subset of ~38,000 subjects randomised before 9 October 2020 with a median follow-up period of 2 months after Dose 2 of BNT162b2 (n=18,860) or placebo (n=18,846).

Demographic characteristics are considered well balanced between vaccine and placebo arm (median follow up 2 months). Subjects were mostly white (83%) and had a median age of 52 years. The younger and older age groups included 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Gender was balanced (51% male). Of note, 35% of individuals were obese in study arms. The demographic distribution was different between seropositive and seronegative individuals, with a median age of 43 years in seropositive and of 52 years in seronegative subjects. Furthermore, the seropositive group covered a higher rate of obese individuals (42.2% versus 34.7%). Demographic characteristics in all participants were roughly comparable to those with median follow up of 2 months.

Charlson co-morbidity diagnoses were balanced in both study arms (20%). Most prevalent co-morbidities were diabetes (7.8%), COPD (7.8%) and malignant disease (3.9% in the vaccine arm and 3.5% in the placebo arm). Other diagnoses accounted for ≤ 1% of subjects in both study arms (median follow up of 2 months).

In the Phase 2/3 study reactogenicity was evaluated in a subset of 8,183 subjects who received BNT162b2 (n=4093) or placebo (n=4090) according to the proposed dosing regimen. The number of subjects aged 16-17 years included in the reactogenicity subset was small (n=8; BNT162b2 n=5; placebo n=3). After each dose, all subjects were asked to report any local reactions, systemic events, and antipyretic/pain medication usage for 7 days, by using an e-diary.

Pain at the injection site was the most common local reaction reported in the vaccine group, slightly more frequently reported among subjects 16-55 years (~80%) compared to >55 years (~70%). In the placebo group 8-14% reported pain at injection site. In the vaccine group redness and swelling were overall reported at a frequency of 5-7% in both age groups (vs. placebo 0-1%). Use of antipyretic/pain medication was more common after Dose 2 than after Dose 1 in both age groups, and overall slightly lower among subjects >55 years regardless of the dose (younger group: 28% after dose 1 vs 45% after dose 2; older group: 20% vs 38%). The use of antipyretic/pain medication was less common in the placebo group (younger group: 34% after dose 1 vs 23% after dose 2; older group: 23% vs 18%).

Among the systemic reactions, headache and fatigue were the most common events, and the frequency was higher after Dose 2 compared to Dose 1 (16-55 YOA [47% vs 59%]; >55 YOA [34% vs 51%]). Fever also occurred more frequently after Dose 2 (16-55 YOA [4% vs 16%]; >55 YOA [1% vs

[3] Phase I: End of study 28 days after Dose 2.
[4] Phase I: participants enrolled in Phase1 in groups that do not proceed to Phase 2/3 (i.e. other doses than 30 µg) may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

11%]). None of the subjects >55 YOA in the placebo group reported events of fever and 1% of the subjects aged 16-55 years reported fever after the first dose.

Overall, the local and systemic reactions were transient and of short duration (resolved within few days after vaccination), the majority were of mild to moderate intensity, and milder and of slightly lower frequency among older subjects (>55 years of age).

In the group of 19,067 participants with 2 months follow up after dose 2, 21.4% and 12.6% (vaccine vs placebo) of the subjects reported at least one AE. 13.6%/3.6% reported at least 1 related AE. Rates were lower compared to the whole enrolled trial population (26.7% (vaccine) and 12.2% (placebo)).

AEs in subjects with a follow up of at least 2 months belonged most often to the SOCs "General disorders and administration site conditions" (11.9% vs 2.9%), "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%), occurring more often in the vaccine than in the placebo arm. PTs comprised most often vaccine typical reactions, i.e. injection site pain, redness and swelling, fever, chills, fatigue, headache as well as myalgia and arthralgia and malaise. Nausea also occurred more often in the vaccine arm (79 cases, i.e. 0.8%, in vaccine vs. 21 cases, i.e. 0.2%, in placebo). Lymphadenopathy was seen in 0.4% subjects in the vaccine arm (38 cases) vs. 0% in the placebo arm (3 cases).

Severe AEs were reported by a small number of subjects (≤1.1%) and equally distributed between the study arms. No differences were seen between age groups. Frequencies are comparable in the whole enrolled trial population and when stratifying according to serostatus.

Numerical imbalances are observed for several hypersensitivity/immunisation reaction preferred terms (5/3 cases in the ≥ 2 months follow up subset, 13/6 cases in the whole enrolled trial population subset, 4 cases deemed severe (whole enrolled trial population), in the SOC immune system disorders).

Lymphadenopathy, nausea, and hypersensitivity are reported more often with the vaccine arm. For these items there is a reasonable possibility of a causal relation to vaccination and they are as such included in the SmPC section 4.8.

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and among those two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. There are incoming reports of anaphylactoid reactions from ongoing vaccination campaigns. A warning is included in the SmPC addressing the need of adequate emergency material in place at the vaccination site, which is common practice with any vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

Four cases of peripheral facial paralysis were observed in vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole enrolled trial population, however the case of paresis was not considered for this calculation). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days

had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician. Taken together, this was considered to indicate there is a reasonable possibility of a causal relation to the vaccine, and to justify inclusion of peripheral facial paralysis (Bell´s palsy) in the SmPC 4.8 with a frequency as 'rare'.

An imbalance in PT connected to sleep disturbances was noted in the whole enrolled trial population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus in the placebo arm). The occurrence of insomnia may plausibly be due to e.g. local/systemic reactogenicity that may occur after vaccination. The CHMP agreed to include insomnia in section 4.8. of the SmPC.

A slight imbalance of hyperhidrosis/night sweats was noted in the whole enrolled trial population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole enrolled trial population). These events may be plausibly associated to the injection of BNT162b2 and should therefore be included in the SmPC section 4.8.

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole enrolled trial population). In addition to pain at injection site, which was commonly reported, pain in the extremity is also considered plausibly related to the vaccination and should therefore be included in the SmPC section 4.8.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole enrolled trial population)), however these are considered not related to study treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm. These were numerically balanced in frequency between vaccine and placebo arm. Autoimmune events will be monitored post-authorisation as described in the RMP.

SAEs occurred at a low frequency in both BNT162b2 and the placebo group (0.6%, 56 cases in vaccine vs. 53 cases in placebo) in subjects with ≥2 months of follow-up post Dose 2, and a similar frequency was observed in the total study population. One SAE of lymphadenopathy and one SAE of shoulder injury were considered related to study intervention. No cases of related SAEs were reported in the adolescent group (only one case of facial bone fracture). Six events of death (2 in the BNT162b2 group and 4 in the placebo group) have been reported in the entire study population, all deemed unrelated to the vaccine.

The rate of subjects discontinuing participation in the study due to AEs was low in both study arms (0.2%/0.1%).

The subgroup of seropositive subjects is limited in size (n=545 BNT162b2; n=580 Placebo). A stratification according to serostatus for AE investigation was specifically performed in individuals with a follow up of at least one month (median Follow up 2 months) and ≥2 months. Most reported SOCs are similar to those identified in the ≥ 2 months population. AE rate in seropositive individuals was lower (22%) compared to seronegative individuals (27%) and no specific safety concern is detected in this subpopulation.

23 participants reported pregnancies in the safety database, nine of them were withdrawn from the study due to the pregnancy status. These participants will be followed up for pregnancy outcomes.

The Applicant has not provided a specific analysis of elderly individuals > 70 years included in the development program. In general, reactogenicity and AE rate were slightly lower in older compared to

younger individuals (stratified according to median age 55 years). Thus, no specific safety concern is anticipated for the elderly.

Data on immunocompromised individuals are limited, which was raised as missing information in the RMP and will be further followed up. 196 participants with stable HIV infection were included in the trial and reported AEs that were mostly reactogenicity-related with no SAEs. No specific safety concern is detected in this subpopulation.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics as applicable.

Assessment of paediatric data on clinical safety

The longest duration of follow-up in the 16-17 years of age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study, albeit is numerically lower (11.6%/4.8%, vaccine/placebo).

The reactogenicity subset included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) show reactogenicity events (local reactions and systemic events) with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

Overall, the safety of BNT162b2 in individuals 16-17 years of age is extrapolated from young adults in general.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.6.11. Conclusions on the clinical safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off (14-Nov-20) included 43,448 subjects who received either two doses of BNT162b2 30µg (n=21 720) or placebo (n=21 728). Overall, the reported reactogenicity profile are in line with any authorised vaccine. In addition, the frequency of reported AEs and SAEs were low. The emerging safety profile is presently considered favourable. Long term safety data, interaction with other vaccines, data on use in pregnancy and other subgroups (e.g. frail subjects, or subjects with pre-existing autoimmune diseases) are missing at this stage.

The lack of long-term follow up renders the data provided non-comprehensive. Therefore, the delivery of the final C4951001 study report, including a 2-year follow up of the studied population, is classified as a specific obligation in the context of a conditional marketing authorisation.

The plan for the generation of further safety data post authorisation is described in the section below.

2.7. Risk Management Plan

Safety Specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breast feeding Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long term safety data

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the UK and US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for Comirnaty. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post-authorisation safety study.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the PASS.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is

requested. The Applicant commits to conduct a study of the co-administration of Comirnaty with inactivated quadrivalent influenza vaccine.

Data from use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- A **web-based AE reporting portal** will be available for vaccine providers (*e.g.* pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- **Signal detection activities** for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA Vaccine will include routine and specific review of AEs consistent with the AESI list provided in the RMP.
- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.
- Regulatory authority **safety alerts monitoring**, to detect and further investigate potential signals being raised on other areas outside of EU.
- A specific adverse reaction **follow-up questionnaire** intended to capture clinical details about the nature and severity of COVID-19 illness particularly in relation to potential cases of vaccine lack of effect or VAED.

- In addition to routine 6-monthly PSUR production, monthly summary safety reports will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:
    - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
    - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
    - Interval and cumulative number of reports per HLT and SOC;
    - Summary of the designated medical events;
    - Reports per EU country;
    - Exposure data (including age-stratified);
    - Changes to reference safety information in the interval, and current CCDS;
    - Ongoing and closed signals in the interval;
    - AESI reports – numbers and relevant cases;
    - Fatal reports – numbers and relevant cases;
    - Risk/benefit considerations.
- The submission of monthly reports complements the submission of PSURs (requested initially every six months). The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).
- Joint adverse event and product complaint (including available batch/lot information) trending reviews will be conducted routinely by the Applicant.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability from manufacturing to vaccination administration site is crucial to ensure maintenance of the cold-chain as well as for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The Applicant's proposal to ensure traceability include:

- SmPC 4.4 labelling to raise HCP awareness regarding the need to clearly record the name and batch of the vaccine to improve traceability;
- a tracking device on every vaccine shipping container that provides real-time monitoring of GPS location and temperature 24 hours per day, 7 days per week;
- vaccine carton labelling also containing a 2-D barcode which has the batch/lot and expiry embedded within
- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card and peel-off labels (stickers with brand name and lot/batch numbers), acknowledging that each Member State will decided if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the Applicant's commitment that by 31 January 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

- Space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine, and keep it thereafter;
- QR code that links to additional information;
- Adverse event reporting information.

Additional pharmacovigilance activities

The Applicant proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study addressing co-administration with another vaccine) and 5 non-Interventional studies (4 safety and 1 effectiveness):

Study (*study short name, and title)* **Status *(planned/on-going)***	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2				
C4591001 *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Category 3				
C4591011	Assessment of occurrence of safety events of interest, including severe or	Anaphylaxis	Interim reports submission:	30-Jun-2021

Planned	atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		31-Dec-2021
				30-Jun-2022
				31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591012 *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021
				31-Dec-2021
				30-Jun-2022
				31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591010 *Planned*	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review:	31-Jan-2021
			Final CSR submission:	31-Mar-2024

C4591015 *Planned*	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission: Final CSR submission:	28-Feb-2021 30-Apr-2023
C4591014 *Planned*	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	-	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022
C4591018 *Planned*	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission: IA submission:	28-Feb-2021 31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022
ACCESS/VAC4EU *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders	Protocol submission: Final CSR submission:	28-Feb-2021 31-Jan-2024

		Long term safety data.		
Co-administration study with seasonal influenza vaccine *Planned*	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

Non-Interventional Post Approval Safety Studies (4)

The Applicant proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 has been provided.

Additionally, Pfizer, on behalf of the Applicant, will sponsor one or more PASS using secondary electronic health records data sources in Europe based on a master surveillance protocol developed through the ACCESS project.

Two additional studies will be conducted using US data:

- 1 study using secondary data from EHR of active military and their families (C4591011),
- 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) have been provided.

Interventional studies (6)

The Applicant proposes 6 interventional studies, of which 2 are ongoing and 4 are planned.

- **Study C4591001** is an ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. At the time of the data cut-off date in Study C4591001 (14 November 2020), a total of 21,720 participants received at least one dose of the candidate vaccine.
- **Study BNT162-01 Cohort 13** is an ongoing multi-site (Germany), Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in 30 immunocompromised adults.
- **Study C4591015** is a planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID 19 mRNA vaccine.
- **Study C4591018** is a planned study of BNT162b2 in 100 adults receiving a stable dose of immunomodulators for the treatment of stable rheumatoid arthritis (RA), in two cohorts (50 tofacitinib, 50 TNF inhibitors). Subjects will be studied for safety, immunogenicity by neutralizing antibody titer, and evidence of asymptomatic infection by N-antigen antibodies.

- A planned **Phase II safety and immunogenicity study** (Safety and immunogenicity in high risk adults) in up to 150 immunocompromised adults (with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments.
- **Co-administration study with seasonal influenza vaccine** study investigating the safety and immunogenicity of Comirnaty and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Non-Interventional PASS in Pregnancy

The Applicant's proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be very limited; therefore, initially this information will derive from the 4 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in the preceding section. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The Applicant will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. The applicant's commitment and considerations are noted to evaluate pregnancy outcomes in a PASS using established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. Further feasibility analyses are awaited with RMP updates post-approval.

Non-Interventional Post-Approval Effectiveness study (1)

The Applicant will conduct at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. These studies will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups. The studies proposed below are under evaluation as potential commitments; studies are presented by geographical area (US and EU).

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The Applicant included a discussion on potential medication errors which is endorsed:

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID-19 vaccines are available, confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC and further materials for healthcare providers which will be made available to the Member States to be integrated in the national campaign for communication, as needed.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centres will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card will be provided with the pre-printed manufacturer name, dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines.
- Peel-off labels with lot/batch number

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those MSs where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Summary of additional risk minimisation measures

None proposed.

The Applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Important Potential Risks		
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Missing information		
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: No risk minimisation measures.	Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan **version 1.0** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, During the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

The following exemptions from labelling and serialization requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[5] document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

US packaging specific derogations (valid for December ’20 and January ‘21)

All EU Members States (MSs), as well as Norway and Iceland, have agreed to grant a temporary

[5] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

exemption to allow the placing in the EU market of the US packaging, under the following conditions:

a. The validity is only temporary and the MAH shall switch to the EU labelling requirements by February ’21;

b. The US pack will have included a Quick Response (QR) code which the vaccine recipient could scan and gain access to the package leaflet (PL) in his/her national language;

c. The MAH shall supply a separate printed PL in the national language(s) of those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine.

EU packaging specific derogations (from February ’21 onwards)

a. Outer and immediate labelling will be provided in English only.

The MAH shall provide outer and immediate labelling in all EU languages by 2nd Q 2022. This exemption is justified on the deep-frozen storage/shipping requirements and the necessity to label batches ahead of time. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

b. A printed package leaflet will be provided in the national language(s) for those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine. In addition, a QR code printed on the outer label and the PL will provide access to the package leaflet in the national language(s).

The MAH shall provide a printed package leaflet in all EU languages by 2nd Q 2022.

The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

c. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

d. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch from US packaging to EU compliant packs in February 2021.

Exemption from the obligation of serialisation

US packaging specific derogations (valid for December ’20 and January ‘21)

a. It is acceptable that the US pack will be placed in the EU market without serialisation according to the EU FMD requirements. Only the Global Trade Item Number (GTIN) will be common for US & EU and this will be printed on the US pack.

EU packaging specific derogations (from February until March ’21)

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from February until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February '21 and a second by 1st of March '21 referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Safe Handling Guidelines for Dry Ice
- Shipping and Handling Guidelines Brochure
- Preparation and Administration Video
- Storage and Handling Video
- Returning the Thermal Shipping Container video
- How to prepare and Administer Poster
- Traceability and vaccination reminder card
- Returning the thermal Shipping Container brochure
- Dry Ice Replenishment Brochure
- Link to Adverse Event Reaction Reporting

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

As of 1 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

Comirnaty is intended for active immunisation against SARS-CoV-2, thereby preventing COVID-19.

3.1.2. Available therapies and unmet medical need

There is currently no approved vaccine in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

3.1.3. Main clinical studies

The clinical development consists of one FIH phase 1 study (BNT162-01) in younger and older adults (18-55 years and 56-85 years) comparing 4 vaccine candidates, and one pivotal clinical study, C4591001 (or BNT162-02).

The pivotal study is a phase 1/2/3 placebo-controlled, randomised, observer-blind, dose finding, multicentre study performed in the US (start date 4 May 2020), Argentina, Brazil, Turkey, Germany, and South Africa, to evaluate the safety, immunogenicity and efficacy of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy adults. The phase 1 part of the study was designed for dose evaluation of 2 vaccines: BNT162b1 and BNT162b2 in younger (18-55 years) and older (65-85 years) adults. The Phase 2 part was designed to confirm safety and immunogenicity of the selected vaccine, BNT162b2, in the first 360 subjects enrolled in the Phase 2/3 part of the study.

The Phase 2/3 part of the study was designed to enrol up to 43,998 subjects (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (within 19 to 42 days), for an efficacy assessment in addition to safety and exploratory immunogenicity assessments.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test (NAAT) in subjects without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed ≥7 days after Dose 2), and in subjects with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The study was event-driven, i.e. the final efficacy analysis was to be triggered by 162 cases; in practice 170 cases were reached.

3.2. Favourable effects

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS-CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS-CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86.7% (95% CI 68.6, 95).

The efficacy analyses in the all-available efficacy population (including participants who had protocol violations), showed consistent results with those in the primary analysis population. The efficacy analyses using CDC defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

The VE in each demographic subgroup analysed, as defined by age (including subjects >65 years), sex, race, ethnicity, and country and in individuals with comorbidities including obesity, diabetes, hypertension and cardiopulmonary diseases was >90%. In the obese population, VE was 95.4% (CI 95% 86.0%, 99.1%).

VE among 65-74-year-olds was 92.9% (CI95% 53.1%, 99.8%). VE among >75-year-olds was 100% (CI95% -13.1%, 100.0) with 0 cases in the vaccine group and 5 cases in the placebo group. VE among >65 years and at risk of severe COVID-19 was 91.7% (95% 44.2%, 99.8%).

Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, but the number of cases after second dose was very low, 1 case in the vaccine group and 4 cases in placebo group. Counting cases from after dose 1, there were 1 case in the vaccine group and 9 cases in the placebo group.

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral responses after vaccination with 2 doses of BNT162b2 at 30 µg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years), and both in terms of neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a marked boosting effect in both younger and older adults. Responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data.

Study BNT162-01 provides evidence for T cell-mediated immune response, with antigen-induced IFNγ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of vaccine. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults.

The immunogenicity results are only considered supportive at this stage, as no correlate of protection has been established. The immune responses support the need for two doses, as neutralising antibody

levels increased substantially following the second dose compared to the first dose. Cell mediated immune responses were demonstrated in very few subjects in phase 1 but confirm a Th1 dominated cytokine pattern.

3.3. Uncertainties and limitations about favourable effects

Based on the available limited data, no reliable conclusion on the efficacy of the vaccine against severe COVID-19 can be drawn from 7 days after the second dose (secondary endpoint). The estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4%, with a large and negative lower bound CI (95% CI: -124.8%; 96.3%). Only a limited number of events occurred at the cut-off date of analysis (1 and 4 cases in the vaccine and placebo groups respectively). The posterior probability for the true vaccine efficacy ≥ 30% (74.29%) did not meet the pre-specified success criterion. Consequently, the efficacy against the severe disease across subgroups, notably certain populations at high-risk of severe COVID-19 cannot be estimated (elderly and subjects with comorbidities).

Efficacy against asymptomatic infection is not available but, notwithstanding all the limitations, will be assessed through seroconversion of N-binding antibodies in BNT162b2 and placebo recipients who did not experience COVID-19.

The pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from subjects who would be infected after vaccination. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies.

Duration of protection has currently been followed up for approximately 100 days after dose 1. Data on longer term protection are anticipated to the extent that the ongoing phase 3 study can continue as planned with a placebo group. The assessment of efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

There are very limited or no data in immunocompromised subjects and in pregnant women. Efficacy in subjects aged 16-17 years is extrapolated from young adults as no cases of disease were reported in this small group at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group, to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

3.4. Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty.

In Study C4591001, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older. Reactogenicity was evaluated in a subset of 8183 subjects (n=4093 vaccinated; n=4090 placebo) up to 7 days after each dose.

Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups.

Regarding AEs, at least one AE was reported in 21% of the vaccinated subjects and in 13% of the placebo arm. The frequency of severe AEs was low (<1%) in both study arms. The most frequently reported SOC were "General disorders and administration site conditions (11.9% vs 2.9%)", "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%). PTs comprised mainly of vaccine typical reactions such as injection site pain, headache, fever, fatigue, malaise as well as myalgia and arthralgia.

For subjects with a follow-up of ≥2 months, SAE were reported at a low frequency (0.5-0.6%) in both the vaccine and the placebo group, with no clinically meaningful differences by age, baseline serostatus, ethnicity, race or sex. Lymphadenopathy and nausea were reported to occur more often in the vaccine group compared to the placebo group in the whole enrolled trial population (respectively 0.4% and 0.6% higher rate than placebo). Numerical imbalances in reporting were observed for insomnia, injection site pruritus and pain in extremity. Since these are supported by a biologically plausible relation to vaccination, these AEs are reflected in the SmPC.

Acute peripheral paralysis was reported in 4 vs. 0 cases (vaccine vs placebo) in the whole study population, of which 2 cases were deemed related to study treatment (see section 2.6.10). For acute peripheral paralysis, there is a reasonable possibility of a causal relation to vaccination and should therefore be included in the SmPC.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. Three reports of anaphylaxis were identified during vaccination campaigns by the time this report was written.

Few cases of hypersensitivity/immunisation reaction events have been observed with the vaccine (13 vs 6 cases) in the whole study population. Hypersensitivity should be annotated in the SmPC, section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

AEs were slightly lower in subjects seropositive to SARS-CoV-2 at baseline (22% vs. 27% in seronegatives), however the number of such subjects was limited (vaccinated n=558; placebo n=590).

Data on immunocompromised individuals is limited, as only 196 participants with stable HIV infection were included in the study. No specific safety concern was detected.

Data from exposure during pregnancy is very limited. Up to the cut-off date 23 pregnancies have been reported in the Phase 2/3 trial and will be followed up for outcome.

Multiple long-term pharmacoepidemiology safety studies are planned to be conducted in order to confirm the safety profile in the already studied population as well as in a broader population including pregnant, immunocompromised and very elderly subjects.

There is no data available on interaction with other vaccines given in co-administration.

In the Phase 2/3 study, the total number of included subjects aged 16-17 years was smaller compared to other age groups (n=138 BNT162b; n=145 placebo), however no safety concerns were identified.

Uncertainties remain regarding causality association of acute peripheral paralysis to vaccination due to the limited number of cases, which are consistent with background rates. Nevertheless, facial paralysis will be included as an adverse event of special interest (AESI) for pharmacovigilance monitoring and in the active surveillance study protocols.

While apart from facial paralysis, whose aetiology is currently unknown, no possible autoimmune adverse events where identified as causally related to vaccination, rare events of this nature cannot be excluded based on the size of the available data set.

There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines, including Comirnaty, and the characterisation of the immune response does not indicate a risk profile in this regard (Th1 skewed).

This vaccine contains two new components (cationic lipid ALC-0315 and PEGylated liquid ALC-0159) in the LNP, for which there is limited experience. Some uncertainties remain regarding the ALC-0315 long half-life. Regarding PEG related toxicity which is known to depend on the dose, dose frequency, duration of treatment and molecular weight of the PEG protein, immunogenicity is not expected to be an issue due to the low molecular weight of this PEG (<2KDa). The scientific data available at this stage do not raise noticeable concerns regarding immunogenicity or immunotoxicity of the PEG, but current evidence is not definitive.

3.6. Effects Table

Table 20 Effects Table for Comirnaty intended for active immunisation to prevent COVID-19 caused by against SARS-CoV-2 in individuals 16 years of age and older (data cut-off: 14 Nov 2020)

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy	First COVID-19 occurrence from 7	**% (95% CI)**	**95.0** (90.0, 97.9)			

Effect	Short Description	Unit	BNT162b2 (30 µg)		Placebo		Uncertainties / Strength of evidence	References
	days after Dose 2, without prior SARS-COV-2, **overall**	**Cases/** Number of subjects at risk for the endpoint	**8/** 17411		**162/** 17511		Robust data with similar efficacy confirmed in all age sub-groups (16-64YOA, >65YOA, 65-74YOA, >75YOA)	Evaluable efficacy population (7 days post dose 2) - Study C495100
	Patients aged ≥65	**%** **(95% CI)**	**94.7** (66.7, 99.9)					
		Cases/ Number of subjects at risk for the endpoint	**1**/3848		**19**/3880			
Unfavourable Effects								
Lymphadenopathy		% (denominator)	0.3% (n=21720)		0% (N=21728)		Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants
Facial paralysis		Number of cases	4		1			
Hypersensitivity/immunisation reaction		Number of cases	13		6			
			Post dose 1	**Post dose 2**	**Post dose 1**	**Post dose 2**	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
Pain at injection site	16-55 years	%	83%	79%	14%	12%		
	>55 years		71%	66%	9%	8%		
Headache	16-55 years		42%	52%	34%	24%		
	>55 years		25%	39%	18%	14%		
Fatigue	16-55 years		25%	39%	25%	39%		
	>55 years		34%	51%	23%	17%		

Abbreviations:
COVID-19: Coronavirus disease, SARS-CoV-2: Severe Acute Respiratory Syndrome, CI: Confidence Interval

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, substantial efficacy in preventing symptomatic COVID-19 infection has been demonstrated, as well as an acceptable safety profile in a large phase 3 study. Uncertainties relate to the

characterization of active substance and finished product. Given the comparable immunogenicity from 10 to 30µg doses, an impact on efficacy of the acceptance of somewhat lower levels of intact mRNA in the commercial product is not considered likely. Furthermore, based on low levels and biological plausibility, an impact of mRNA impurities on safety is deemed unlikely (see section 3.7.3).

Due to the limited extent of safety follow-up, the delivery of final data from the full 2-year follow up in the pivotal clinical trial are considered important to confirm the current knowledge.

With regards to the balance of efficacy and safety benefits and risks, it is overwhelmingly positive for subjects at risk of severe COVID-19, including the elderly and those with comorbid conditions, which are known to increase the risk of complication and death due to infection.

Uncertainties concerning the pharmaceutical characterization of the commercial product are compatible with a positive benefit/risk balance. This pertains not only to adults but, by extrapolation, to individuals 16-17 years of age.

Data are limited in individuals seropositive against SARS-CoV-2 at baseline. Available data however do not indicate any specific safety concerns, and efficacy is anticipated also in this subset.

There are no data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

Based on biological plausibility no risk in breastfeeding is anticipated.

While there was no indication of an excess risk of severe allergic reactions such as anaphylaxis in the clinical study program, three post marketing cases, of which 2 in patients carrying adrenaline pens and one in a person with no known history of allergies, have been reported during vaccination campaigns, and all resolved with standard treatment. Hypersensitivity to the active substance or to any of the excipients is a contraindication. However, there is presently no substantial evidence of a negative benefit/risk balance in a subject with severe allergy to substances absent in the vaccine. For all subjects, the vaccine should be administered in settings where resuscitation facilities are available, as specified in the SmPC and in line with other vaccines. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19.

Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned.

3.7.2. Balance of benefits and risks

Overall, the available data are supportive of a positive B/R in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation in the context of a conditional MA, including further characterisation of the active substance and finished product, the continuation of the pivotal study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine (Process 1). The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities.

Data demonstrates the presence of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are not sufficiently characterised, and although the limited data provided for protein expression does not fully address uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein, the amount of any such proteins, is expected to be too low to elicit an immune response of biological relevance.

Indeed, considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell it cannot be excluded that different proteins than the intact full-length spike will be expressed. The risk of unwanted immunological events is considered low based on the following observations and considerations:

- Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
- The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA able to be translated into a specific protein or peptide.
- The level of any individual fragment of mRNA species would anyway be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the truncated proteins would be non-significant.

Also, lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

Regarding the proposed control strategy for active substance and finished product, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Considering the above and the current public health emergency, the characterisation of the active substance and finished product are considered acceptable, and the proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA.

Therefore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the Applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between March and July 2021.
Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomized, placebo-controlled, observer-blind study C4591001 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of Comirnaty.

- Unmet medical needs will be addressed

There is no approved or widely available COVID-19 vaccine, and COVID-19 remains associated with substantial morbidity and mortality. While care for patients who have COVID-19 has improved over time and with clinical experience, no medications to cure COVID-19 are available and there remains an urgent need for a prophylactic vaccine during the ongoing pandemic.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence including the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit/risk balance of Comirnaty is positive.

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Comirnaty is favourable in the following indication:

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.